THE INFLUENCE OF PHYSICAL ACTIVITY, SEDENTARY TIME, AND ADIPOSITY, ON BEHAVIORAL AND NEUROELECTRIC MEASURES OF ATTENTIONAL INHIBITION

BY

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THESIS

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ABSTRACT

Physical inactivity and excess adiposity are thought to be detrimental not only to physical but cognitive health as well. However, the cognitive implications of these interrelated health factors are rarely examined together, therefore, little is known regarding the concomitant contribution of physical activity and adiposity to cognition. Furthermore, time spent being sedentary, known to be distinct from low physical activity, is a public health concern given its propensity to exacerbate the health implications of inactivity on both physical and mental health. However, the association between sedentary time and cognition remains unknown. The research presented herein sought to examine the relationship between objectively measured physical activity, adiposity, sedentary time, and behavioral and neuroelectric indices of cognitive control among 25-45 year olds. Percent of time spent engaging in moderate-to-vigorous physical activity (MVPA) and sedentary behaviors (%Sedentary) was monitored using an accelerometer worn for at least 4 days (minimum 8 hours/day). Whole body adiposity (%Fat) was assessed using Dual Energy X-ray Absorptiometry (DXA). Attentional inhibition, a component of cognitive control, was assessed using a modified Eriksen Flanker task. Neuroelectric function was assessed using event-related brain potentials. Specifically, the changes (incongruent - congruent task conditions) in amplitude of the P3 waveform in a central-parietal region of interest (ROI) was used to index the ability for modulation of attentional inhibition. After adjusting for significant covariates (age, sex, and intelligence quotient), %MVPA was a positive predictor of accuracy in the incongruent condition of the Flanker task ($\beta = 0.31$, $P = 0.03$), signifying that individuals who engaged in greater physical activity exhibited superior attentional inhibition. Additionally, results showed an interaction effect of %Fat and %MVPA attentional inhibition ($\beta = 0.45$, $P = 0.04$), suggesting that individuals with lower chronic activity and greater adiposity exhibited poorer attentional

inhibition. The positive influence for physical activity on cognitive control persists even following the adjustment of demographical variables, intellectual ability, and adiposity. Neuroelectrically, %Sedentary time was inversely related to the difference in the ROI mean amplitude, whereby participants who spent more time being sedentary exhibited poorer ability to flexibly modulate attentional resources in response to greater task demands. Given that most adults spend much of their day engaging in sedentary behaviors, these findings provide support for public health initiatives to decrease sedentary behaviors and increase MVPA in order to prevent decrements in both physical and cognitive health.

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TABLE OF CONTENTS

CHAPTER 1: INTRODUCTION 1

1.1 Purpose 6

1.2 Hypotheses 6

CHAPTER 2: LITERATURE REVIEW 7

2.1 Overview 7

2.2 Cognitive Control and Attentional Inhibition 7

2.3 Event-Related Brain Potentials 9

2.4 Physical and Behavioral Effects on Cognitive Control 10

CHAPTER 3: STUDY 1 METHODOLOGY 18

3.1 Participants 18

3.2 Procedures 19

3.3 Measures 20

3.4 Statistical Analysis 22

CHAPTER 4: STUDY 1 RESULTS 24

4.1 Participant Demographics 24

4.2 Bivariate Correlations 24

4.3 Hierarchical Linear Regression Analysis 26

4.4 Independent Samples T-Test 27

CHAPTER 5: STUDY 2 METHODOLOGY 29

5.1 Participants 29

5.2 Procedures 30

5.3 Measures 31
5.4 Statistical Analysis 34
CHAPTER 6: STUDY 2 RESULTS 35
6.1 Participant Demographics 35
6.2 Bivariate Correlations 35
6.3 Hierarchical Linear Regression Analysis 37
6.4 ANOVA Analysis 40
CHAPTER 7: DISCUSSION 43
7.1 Study 1 43
7.2 Study 2 45
7.3 Limitations 49
7.4 Conclusions 50
REFERENCES 52
APPENDIX A: INFORMED CONSENT 65

CHAPTER 1: INTRODUCTION

Over the last few decades, physical inactivity has emerged as a major public health concern across the globe (Hallal et al., 2012). Modern daily life, particularly in industrialized societies like the United States, is characterized by decreased opportunities for physical activity along with the abundant supply of energy-dense and nutritionally poor foods. Sedentary lifestyles have increasingly become the norm, as the technological comforts of modern society afford us the opportunity to be inactive for large portions of the day. Consequently, physical activity has been gradually phased out of our daily lives, while the demand for maintenance of cognitive performance throughout the day has remained constant. This is problematic given that physical activity has been previously shown to have positive benefits on cognitive function, particularly cognitive control processes (Booth et al., 2013; Kerr et al., 2013). Experimental data from animal models provides causal evidence for the importance of physical activity for learning and memory as well as neurogenesis (Gomez-Pinilla, Vaynman, & Ying, 2008; van Praag, Christie, Sejnowski, & Gage, 1999). Although experimental data in humans is limited, randomized controlled trials have demonstrated benefits of engaging in physical activity for cognitive function and brain health among children and adults (Erickson et al., 2011; Hillman et al., 2014). Cognitive control (a component of executive function) may be of particular importance to this area because it encompasses cognitive processes that are thought to drive goal-directed behavior and allow us to adopt to changing environmental demands (Best & Miller, 2010). Further, increases in physical activity and aerobic fitness have been linked to improved cognition, with disproportionately greater increases in cognitive control (Colcombe & Kramer, 2003; Hillman, Erickson, & Kramer, 2008).

These chronically low levels of physical activity are concerning because people who are less physically active are more likely to have shorter lifespans and have an increased risk for heart disease, stroke, diabetes mellitus type 2, depression, and some cancers (Bize, Johnson, & Plotnikoff, 2007). Further, the overall reduction in the quantity of physical activity is thought to be an important contributor to the persistently elevated prevalence of obesity among US adults, currently at 35%, and its associated comorbidities (Flegal, Kruszon-Moran, Carroll, Fryar, & Ogden, 2016; Pate, Taverno Ross, Liese, & Dowda, 2015). There is an abundance of evidence implicating excess adiposity in increased metabolic health risks, diabetes mellitus type 2, coronary heart disease, increased incidence of certain forms of cancer, decreased life span, obstructive sleep apnea, and osteoarthritis (Kopelman, 2000). In addition to evidence linking excess fat mass to increased chronic disease risk, there is accumulating evidence indicating excess fat mass is related to decreases in cognitive performance, along with risk for cognitive decline in older age (Smith, Hay, Campbell, & Trollor, 2011; Whitmer et al., 2008). Increased adiposity in adults has also been shown to be related to lower grey matter volume (Walther, Birdsill, Glisky, & Ryan, 2009), reduced processing speed (Sanz et al., 2013), reduced synaptic plasticity (Erion et al., 2014), and an increased risk for dementia (Whitmer, Gunderson, Barrett-Connor, Quesenberry, & Yaffe, 2005).

Cognitive control processes may be of particular significance in this area since they enable us to adjust our behavior to changing environmental demands (Best & Miller, 2010). The core processes of cognitive control comprise attentional inhibition (the ability to resist distractions to maintain focus), working memory (the ability to store, maintain, and manipulate information to be retrieved within a brief period), and cognitive flexibility (the ability to shift attention, select information, and alter response strategy in response to changing task demands)

(Diamond, 2013). Human studies have illustrated differences in cognitive control performance across levels of cardiorespiratory fitness in both children and older adults (Hillman et al., 2006; Khan & Hillman, 2014; Wong et al., 2015). Interestingly, while fitness training has been shown to have multiple benefits on different cognitive domains, in adults, the magnitude of fitness-derived benefits appear to be greatest for cognitive control processes (Colcombe & Kramer, 2003), indicating that cognitive control processes may be particularly susceptible to lifestyle modification.

Virtually all the literature has focused on the role of physical activity on cognitive control, resulting in a dearth of knowledge on the role of sedentary behavior on specific aspects of cognitive function. Current scientific work suggests that sedentary time is behaviorally different from exercise and moderate to vigorous physical activity (MVPA) (Voss, Carr, Clark, & Weng, 2014). These findings suggest that sedentary behavior has separate risk factors, like increased all-cause mortality (Katzmarzyk, Church, Craig, & Bouchard, 2009; van der Ploeg, Chey, Korda, Banks, & Bauman, 2012), depression and anxiety (de Wit, van Straten, Lamers, Cuijpers, & Penninx, 2011), and diabetes mellitus type 2 (Grøntved & Hu, 2011), that are independent of the amount of physical activity a person engages in. A person can both engage in the recommended 150 min/week MVPA, and still spend the same amount of time being sedentary as someone who does not meet those recommendations (Craft et al., 2012). However, to date, most of the scientific literature has focused on how MVPA affects cognitive function, while little has been done to investigate the effects of sedentary time on cognition or brain health (Rhodes, Mark, & Temmel, 2012). Since sedentary time comprises such large portions of a typical day (Matthews et al., 2008), it may have a greater potential to influence cognitive function. For example, exercise typically only accounts for 2-5% of the waking day (Dunstan,

Howard, Healy, & Owen, 2012) and is performed by a small portion of the population (Troiano et al., 2008). On the other hand, sedentary time may account for around 64.5% of waking hours (Unick et al., 2017). Given that sedentary time and MVPA are independent, they may have differential impacts on the brain. Research to determine the direct impact of sedentary time on cognition, after accounting for the effects of MVPA, is necessary. If there are overlapping pathways between the positive effects of MVPA and the negative effects of sedentary behavior, then sedentary behavior may counteract the benefits of daily MVPA on the brain. Conversely, sedentary time may negatively influence the brain through pathways that are independent of the positive effects seen with physical activity, leading to simultaneous, competing effects on cognition. Such findings would have a great impact on the current physical activity recommendations for improving cognitive performance.

Given that the positive influence of physical activity can be selective for particular cognitive domains, the work presented herein focused on attentional inhibition, an important component of cognitive control. Specifically, the Eriksen flanker task (Eriksen & Eriksen, 1974) has often been used to measure attentional inhibition. In addition to task performance measures (i.e., response time, response accuracy), which are routinely used in cognition research, event-related potentials (ERPs), electroencephalographic (EEG) activity evoked by events in the stimulus-response environment, are useful in deciphering aspects of cognition that are influenced by physical activity participation. One prominent component of an ERP in the stimulus-locked waveform is the P3 (or P300), which is a positive-going component that occurs approximately 300-600ms following the presentation of a stimulus. The amplitude of this component has been related to the amount of attentional resources allocated toward the stimulus, while the latency is thought to be a metric of stimulus processing speed (Polich & Kok, 1995). It is widely thought

that, relative to the congruent condition, the incongruent task condition of the Eriksen Flanker task elicits a greater amount of interference control requiring the participant to upregulate or dedicate larger amounts of attentional inhibition to maintain task performance. Importantly, previous work in older adults has shown that physical activity is positively related to superior attentional inhibition as well as greater P3 amplitude and faster P3 latency (Hillman, Belopolsky, Snook, Kramer, & McAuley, 2004). Therefore, behavioral performance metrics and neuroelectric indices accompanying the flanker task have been shown to exhibit sensitivity to change following the provision of physical activity.

Although there is an abundance of literature demonstrating the benefits of exercise training and greater aerobic fitness on cognitive functioning, the independent or overlapping implications of habitual physical activity and adiposity on selective aspects of cognitive control remains equivocal. Few studies (Chang, Chu, Chen, Hung, & Etnier, 2016) have attempted to determine whether any influence of physical activity or adiposity on cognitive control is independent or shared. Likewise, the implications of habitual sedentary behaviors on selective aspects of attentional inhibition remain unclear. It is unknown whether any connection between sedentary time and attentional inhibition is free of the influence of adiposity or habitual physical activity.

Accordingly, study 1 aimed to investigate the relationship between objective measures of physical activity, adiposity, and attentional inhibition, a component of cognitive control, among adults and Study 2 aimed to investigate the relationship between objective measures of sedentary time and behavioral and neuroelectric measures of attentional inhibition while accounting for the effect of adiposity and MVPA.

1.1. PURPOSE

The purpose of the proposed studies was to 1) investigate the relationship between objective measures of physical activity, adiposity, and attentional inhibition and 2) investigate the relationship between objectively measured sedentary time and task performance and neuroelectric indices of attentional inhibition while accounting for the effect of adiposity and physical activity.

1.2. HYPOTHESES

It was hypothesized that 1) habitual physical activity and adiposity would be differentially related to behavioral measures of attentional inhibition, after controlling for significant demographic variables and intellectual ability and 2) time spent being sedentary would exhibit a negative relationship with attentional inhibition after accounting for adiposity and physical activity. Participants who engaged in greater amounts of MVPA were expected to perform better on tasks of attentional inhibition, replicating earlier research (Booth et al., 2013; Hillman et al., 2006). Additionally, it was expected that there would be an observed inverse relationship between attentional inhibition and adiposity, as previously exhibited (Gunstad et al., 2007; Nguyen, Killcross, & Jenkins, 2014; Smith et al., 2011). Finally, sedentary participants were expected to exhibit longer P3 latency and smaller P3 amplitude, indicating slower cognitive processing speed and lesser allocation of attentional resources, respectively. More specifically, it was thought that time spent being sedentary would be inversely related to the ability to modulate attentional resources as task demands increased, as measured by P3 mean amplitude difference during a task requiring variable amounts of attentional inhibition.

CHAPTER 2: LITERATURE REVIEW

2.1. OVERVIEW

A growing body of literature has emerged suggesting that habitual physical activity is one major factor which may help to ward off lifestyle diseases like obesity and diabetes mellitus type 2. Despite mounting evidence leading researchers to believe that physical activity is important in daily life, only 32% of adults engage in regular MVPA for 20 minutes or more on three or more occasions per week in the United States (National Center for Health Statistics, 2012). Further, recent evidence has indicated that the decrease in physical activity, and related increase in obesity, negatively impacts cognitive performance in both children and adults. Specifically, research has shown that decreased physical activity is disproportionately linked to decrements in cognitive control (Colcombe & Kramer, 2003; Hillman et al., 2008). Using behavioral measures of cognitive control, fMRI, and ERPs, researchers have started to study the effects of physical activity, adiposity, and sedentary time on multiple measures of cognitive function.

2.2. COGNITIVE CONTROL AND ATTENTIONAL INHIBITION

When researchers explore how physical activity, adiposity, and sedentary behaviors are related to cognition, many different types of paradigms, tapping into several different aspects of cognition, have been investigated. Colcolmbe and Kramer (2003) observed that the greatest benefits associated with physical activity and fitness are found for cognitive control. Similarly, research conducted by Booth, Kerr, and Hillman (Booth et al., 2013; Hillman et al., 2014; Kerr et al., 2013) have all shown similar benefits of increased physical activity for cognitive control. Often times, researchers investigating the relationship between obesity and cognition focuses their efforts on the effects on cognitive control as well (Nguyen et al., 2014; Sanz et al., 2013).

Cognitive control refers to an overarching set of cognitive processes involved in the regulation of goal-directed behavior (Botvinick, Braver, Barch, Carter, & Cohen, 2001; Norman & Shallice, 1986) and allow us to adopt to changing environmental demands (Best & Miller, 2010).

The core cognitive components, collectively deemed cognitive control, are attentional inhibition (the ability to resist distractions to maintain focus), working memory (the ability to store, maintain, and manipulate information to be retrieved within a brief period), and cognitive flexibility (the ability to shift attention, select information, and alter response strategy in response to changing task demands; Diamond, 2013). Attentional inhibition refers to the ability to ignore distracters and selectively focus on relevant aspects of the stimulus environment. Working memory is the ability to hold and manipulate information in short durations. Lastly, cognitive flexibility refers to the process of efficiently switching between behaviors (Diamond, 2013). Of the core processes of cognitive control, attentional inhibition has been the most studied by physical activity researchers, and to a lesser extent body composition researchers as well (Gunstad et al., 2007; Hillman et al., 2014, 2004; Kamijo et al., 2014; Smith et al., 2011). Diamond (2012) argues that executive functions, and therefore attentional inhibition, are crucial for school and job success. In the modern workplace it is essential to control one's behavior by overriding impulses and exercising discipline to not act inappropriately, providing support for the importance of increasing attentional inhibition in everyday life.

2.2.1. Flanker Task

One task often used to measure attentional inhibition is the Eriksen Flanker task (Eriksen & Eriksen, 1974). The task requires participants to utilize varying amounts of attentional inhibition through the different conditions used (i.e., congruent and incongruent). The Flanker task requires an individual to pay attention to a centrally located target arrow presented amid an

array of four task-irrelevant distractor arrows flanking the target on both sides. Typically, congruent stimuli (e.g., <<<<< or >>>>>) result in faster and more accurate responses, while incongruent stimuli (e.g., <<><< or >><>>) result in slower and less accurate responses, due to the centralized target and flanking stimuli activating multiple (opposing) action-schemas (Erikson & Schultz, 1979). That is, during the incongruent condition, both correct and incorrect response-mappings are activated due to the centralized stimulus and the flanking stimuli, respectively. Thus, these trials require greater amounts of attentional inhibition as individuals must inhibit the flanking stimuli to execute the correct response (Spencer & Coles, 1999).

2.3. EVENT-RELATED BRAIN POTENTIALS

Behavioral task performance has helped researchers describe individual and group performance on a variety of cognitive tasks. However, these measures do not provide us with a way to look at the function of the brain during these tasks. Beyond the assessment of an individual's responses, event-related brain potentials (ERPs) provide a way to gain insight into the underlying mechanisms and neuronal activity behind an individual's overt action. This allows for assessment of some of the brain processes that occur between the stimulus onset and a participant's response. ERPs are a class of EEG activity that occurs in response to, or in preparation for, a stimulus or response (Fabiani, Gratton, & Coles, 2000). EEG is a method for recording differences in electrical potentials between various regions of the scalp, where the neuroelectric activity reflects synchronous firing of large groups of neurons. This neuronal activity can reflect both exogenous (i.e., independent components that are triggered by the presence of a stimuli, not the cognitive processing of said stimuli) or endogenous processes (i.e., higher-order cognitive processes that are entirely task dependent) (Luck, 2005a).

2.3.1. P3 Component

The P3 (also known as the P300) component of ERPs is an endogenous component of the stimulus-locked waveform that has garnered significant attention in the physical activity and exercise literature. The P3 is a positive going deflection, with a topographic maximum over the central-parietal region of the cortex, which occurs between 300 and 600 milliseconds following the presentation of a stimulus (Polich & Kok, 1995). The P3 is sensitive to the amount of attentional resources engaged during task performance. Usually, as task difficulty increases, P3 amplitude also increases. Amplitude is believed to reflect the amount of attentional resources that have been allocated to a given stimulus, and is measured as the change in voltage from the pre-stimulus baseline to the largest positive peak (Polich, 2007). Therefore, an increase in amplitude is thought to reflect an increase in attentional resources that are allocated to a stimulus. The difference in amplitude between two conditions is known as the amplitude difference, and reflects an upregulation in resource allocation following increased task demands. The mean amplitude is often used for this difference, as the peak amplitude is biased by the number of trials used in analysis (Luck, 2005b). The latency is believed to reflect stimulus classification or cognitive processing speed, and is measured from the stimulus onset to the maximum peak (Polich & Kok, 1995).

2.4. PHYSICAL AND BEHAVIORAL EFFECTS ON COGNITIVE CONTROL

2.4.1.Physical Activity and Cognitive Control

Decreased physical activity has both a physical and economic impact on individuals in the United States due to the high medical costs associated with the debilitative diseases that physical inactivity causes (Bize et al., 2007). Additionally, there is a large body of literature that

links physical activity with improvements in brain function and cognition. Substantial support for the importance of physical activity for cognitive function can be found in rodent studies, where animals with environments enriched with exercise equipment (e.g., running wheels, climbing boxes, etc.) showed improvements in learning and memory, demonstrating that physical activity is directly related to neurogenesis and neurotrophic growth factors (Gomez-Pinilla et al., 2008; van Praag et al., 1999). These findings indicate that physically active behaviors may influence the neural underpinnings of cognitive function.

In addition to rises in neurogenesis associated with physical activity, cerebrovascular remodeling has also been demonstrated in response to regular physical activity. Cerebrovascular remodeling refers to the structural (angiogenesis) or functional (endothelial function) changes in the arterial vasculature of the brain. During MVPA and exercise, global cerebral blood flow (CBF) is relatively constant, however regional CBF increases due to increased neural and metabolic activity. Regional CBF rises in areas of the brain that are more active during exercise, and thus require greater amounts of oxygen and glucose to function. As CBF increases in specific regions, endothelial cells experience shear stress, signaling mechanoreceptors and chemoreceptors of the endothelium (Szostak & Laurant, 2011). In short, this increased CBF from MVPA and exercise lead to arteriogenesis and angiogenesis in more active regions of the brain.

Physical activity's stimulation of angiogenesis is important for the brain, and specifically neurogenesis, as it is thought that cerebrovascular remodeling functions to accommodate the increased nutrient demands of neural tissue following neurogenesis, which helps newly born neurons integrate into existing learning and memory circuits (Goldman & Chen, 2011). While human work on this subject is sparse, one study demonstrated that 12 weeks of chronic exercise training in humans results in increased cerebrovascular blood flow in the dentate gyrus, which

correlated with improvements in rate of learning in hippocampus dependent tasks (Pereira et al., 2007).

Furthermore, it has become widely accepted that physical activity and cardiovascular fitness may aid aspects of cognition and may attenuate cognitive decline; however, cognitive control seems to be enhanced to a greater extent than other forms of cognition (Colcombe et al., 2004; Hall, Smith, & Keele, 2001; Voss et al., 2013). Numerous studies have led to the conclusion that increasing cardiovascular fitness, through increases in daily physical activity, may have the ability to enhance cognition among children and adults (Colcombe & Kramer, 2003; Erickson et al., 2011; Hillman et al., 2014; Kerr et al., 2013). Through this research, it seems that there is a positive effect of physical activity on cognitive ability. Much of the research on physical activity and cognition has indicated that cardiovascular fitness has a facilitative effect on cognitive control across the lifespan (Buck, Hillman, & Castelli, 2008; Castelli, Hillman, Buck, & Erwin, 2007; Hillman et al., 2004). Additional research has shown that participants who engaged in greater amounts of MVPA performed better on measures of attentional inhibition (Booth et al., 2013; Hillman et al., 2006). Therefore, cognitive control may be enhanced through improved cardiovascular fitness, simply by increased physical activity levels.

Along with numerous studies that have examined behavioral changes in response to physical activity, brain activity has also been examined by analyzing ERPs and fMRI. These studies have sought to reveal the relationships between physical activity and individual differences in regional brain activity during task performance in both children and adult populations (Hayes, Hayes, Cadden, & Verfaellie, 2013; Hillman et al., 2008). One study conducted by Chaddock-Heyman and colleagues (Chaddock-Heyman et al., 2013) found that

children who had completed a 9-month exercise intervention did not differ from young adults on tasks of attentional inhibition. This finding was in stark contrast to the results of children in a wait-list control group, where children showed significantly lower accuracy rates than young adults, indicating that a 9-month physical activity intervention helped to increase behavioral performance on attentional inhibition tasks. Utilizing fMRI, results showed that those children in the control group exhibited a significant decrease in right anterior prefrontal cortex activation, suggesting that exercise enhanced attentional inhibition is facilitated by the prefrontal cortex.

Additional research by Colcombe and collogues (Colcombe et al., 2004) demonstrated that both higher-fit and aerobically trained individuals had greater task-related activation during the measures of attentional inhibition, when compared to lower-fit or non-aerobic trained controls. Task-based studies using both ERP and fMRI suggest that physical activity may be associated with altered PFC function, which may be a mechanism for improved performance on tasks that require cognitive control.

2.4.2.Obesity and Cognitive Control

Over the past few decades, physical inactivity has become a significant public health concern (Hallal et al., 2012). These chronically low levels of physical activity are thought to be an important contributor to the high rate of obesity in America, currently at 35%, and its associated comorbidities (Flegal et al., 2016; Pate et al., 2015). Research has shown an abundance of evidence implicating excess adiposity with compromised metabolic health and higher chronic disease risk, including increased metabolic health risks, diabetes mellitus type 2, coronary heart disease, increased incidence of certain forms of cancer, decreased life span, obstructive sleep apnea, and osteoarthritis to name a few (Kopelman, 2000). Lately, there have

been increased instances of research linking obesity and excess fat mass to decrements in cognitive performance.

Recent research suggests that increased adiposity is associated with poor cognitive performance, independent of the medical issues associated with obesity. Across multiple studies, research has shown that obesity is associated with cognitive deficits, especially in cognitive control (Smith et al., 2011). These deficits in cognitive performance are seen in all age ranges as well, spanning from young children (Khan et al., 2015; Li, Dai, Jackson, & Zhang, 2008) to older adults (Elias, Elias, Sullivan, Wolf, & D'Agostino, 2003; Walther et al., 2009). These results are consistent with previous research studies that observed cognitive control is inversely related to adiposity (Gunstad et al., 2007; Nguyen et al., 2014; Smith et al., 2011). Obesity has been shown to be related to neurostructural deficits in the prefrontal and orbitofrontal cortices and in the frontal-subcortical activation of cognitive function as well (Barkin, 2013; Stanek et al., 2011). However, comparatively less is known regarding the role of adiposity or excess fat mass on behavioral and neuroelectric indices of attentional inhibition. A select few studies in children have examined differences in ERP components and demonstrated that obese children exhibit lapses in error monitoring and differential patterns in error-related negativity (Kamijo et al., 2014). Specific to the P3, obese children exhibit longer P3 latencies and lower amplitudes, relative to their healthy weight counterparts (Tascilar et al., 2011). Converging evidence suggests that obesity has a negative relationship with cognitive performance, both in kids and adults, and that this negative relationship may be particularly robust for cognitive control processes.

2.4.3.Sedentary Behavior and Cognitive Control

It is generally understood that regular MVPA is good for your body and brain, however, modern daily life is characterized by decreased opportunities for physical activity. Inactive

lifestyles have increasingly become the norm, leading to increased sedentary behaviors in daily life. Given this trend towards physical inactivity, it is surprising the scarcity of literature exploring the relationship between sedentary time and cognition (Rhodes et al., 2012). Virtually all the aforementioned literature has focused on the role of physical activity or obesity on cognitive control, with very little exploration into the role of sedentary behavior on cognitive function.

Current scientific work suggests that sedentary time is behaviorally different from exercise and MVPA (Voss et al., 2014), resulting in separate risk factors, like increased all-cause mortality, depression, anxiety, and diabetes mellitus type 2 (de Wit et al., 2011; Grøntved & Hu, 2011; Katzmarzyk et al., 2009; van der Ploeg et al., 2012). These risk factors are independent of the amount of physical activity a person engages in; a person can both engage in the recommended 150 min/week MVPA, and still spend the same amount of time being sedentary as someone who does not meet those recommendations (Craft et al., 2012). Physical activity typically only accounts for 2-5% of the waking day, while sedentary time may account for around 64.5% of waking hours (Unick et al., 2017). Given that sedentary time and MVPA are independent, they may have differential impacts on the brain. Since sedentary time comprises such large portions of a typical day, it may have a greater potential to influence cognitive function as well.

As stated previously, there is a great deal of support for the importance of physical activity for cognitive function in rodent studies. Multiple studies have shown increased neurogenesis in animals that were exposed to exercise equipment (e.g., running wheels, climbing boxes) (Gomez-Pinilla et al., 2008; van Praag et al., 1999). However, it is important to note that enhanced neurogenesis in the exercise group is in comparison to a more sedentary control.

Therefore, it may be that the lack of neurogenesis seen in control animals is an outcome of extensive inactivity, in contrast to an increase in neurogenesis being related to increased physical activity.

Endogenous growth factors play multiple roles that facilitate the survival and maturation of new neurons, which is critical for neurogenesis, synaptic plasticity, and angiogenesis. In particular, brain derived neurotropic factor (BDNF) and insulin-like growth factor (IGF-1) are particularly involved with the positive effects of exercise on the brain and cognition (Cotman, Berchtold, & Christie, 2007). While the effect of sedentary behavior on growth factors has not been studied directly, there are a few potential pathways through which sedentary behaviors may influence neurogenesis. Sedentary time may impair IGF-1 and BDNF signaling in the brain, given that IGF-1 and insulin share some receptor and signaling pathways (Blakesley, Scrimgeour, Esposito, & Le Roith, 1996). Since insulin sensitivity is disrupted shortly after prolonged sedentary behavior (Stephens, Granados, Zderic, Hamilton, & Braun, 2011), over-abundance of insulin may suppress IGF-1 signaling due to their shared pathways, which in turn would impair IGF-1 signaling in the brain, reducing neuronal growth and repair (Messier & Teutenberg, 2005). The disruption of IGF-1 signaling can also disrupt its normal modulation of BDNF, which compounded with the already reduced IGF-1 signaling, would slow neurogenesis and impair synaptic plasticity, both of which are modulated by BDNF (Gomez-Pinilla et al., 2008).

In sum, there seems to be an overall consensus indicating that cognitive function is positively related to physical activity, in everyone from young children to the elderly. Additionally, there is a growing agreement among scientists that increased adiposity and obesity are negatively related to cognition, particularly cognitive control processes. However,

surprisingly little knowledge exists concerning the relationship between sedentary behaviors and cognitive function.

CHAPTER 3: STUDY 1 METHODOLOGY

3.1. PARTICIPANTS

Seventy-nine adult subjects between the ages of 25-45 years participated in the study. Participants were recruited from the East-Central region of Illinois from two on-going trials (The Human Gut-Microbiota-Brain Project and Investigating the Effects of Avocado Intake on Metabolism and Cognition: A Systems Approach (NCT02740439)) at baseline. Written informed consent in accordance with the University of Illinois Institutional Review Board was obtained. Participants were excluded if they had a history of neurological disease, use of anti-psychotic or anti-anxiety medication, and chronic metabolic diseases. Intelligence quotient (IQ) was evaluated using the Kaufman Brief Intelligence Test 2 (K-BIT2). Table 1 lists participants' inclusion-exclusion criteria. Briefly, participants were excluded from analysis for incomplete body composition (n=2) or habitual physical activity data (n=6), or if they were outliers (± > 3 *SD*) on measures of cognitive control (n = 6). Therefore, analyses were conducted on a final sample of 65 subjects (26 males, 39 females).

Table 1

Inclusion-Exclusion Criteria for Participants

Inclusion	Exclusion
1. 25-45 years of age	Below 25 or above 45 years of age
2. No history of neurological or gastrointestinal disease	Any reported neurological or gastrointestinal disease (i.e. Cardiovascular disease, ADHD)
3. Complete body composition scan	Unable to complete DXA scan
4. Wear habitual physical activity monitor	Insufficient wear time of the accelerometer (minimum 480 minutes per day for 4 out of 7 possible wear days)
5. Perform cognitive tasks within ± 3 SD of the mean for accuracy in all task conditions	Performance below 85% accuracy in any cognitive task or task condition

3.2. PROCEDURES

Participants visited the laboratory on two non-consecutive days. On the first visit, participants completed the informed consent, and were then screened using a medical history and demographic questionnaire. Utilizing the demographic questionnaire, participants were categorized into three levels of socioeconomic status (SES) (Low: $0-$29,999; Middle: $30,000-$69,000; High: >$70,000) based on their total household income. Following screening, intelligence quotient (IQ) was evaluated using the Kaufman Brief Intelligence Test 2 (K-BIT2) based on the age-normed standardized IQ exam, administered by trained experimenters. Next, participants completed a whole body DXA scan to assess adiposity, and height and weight were assessed using a stadiometer (model 240; SECA, Hamburg, Germany) and a digital scale (WB-300 Plus; Tanita, Tokyo, Japan), respectively. At the conclusion of testing session one, participants were given an accelerometer and instructed on proper wear procedures.

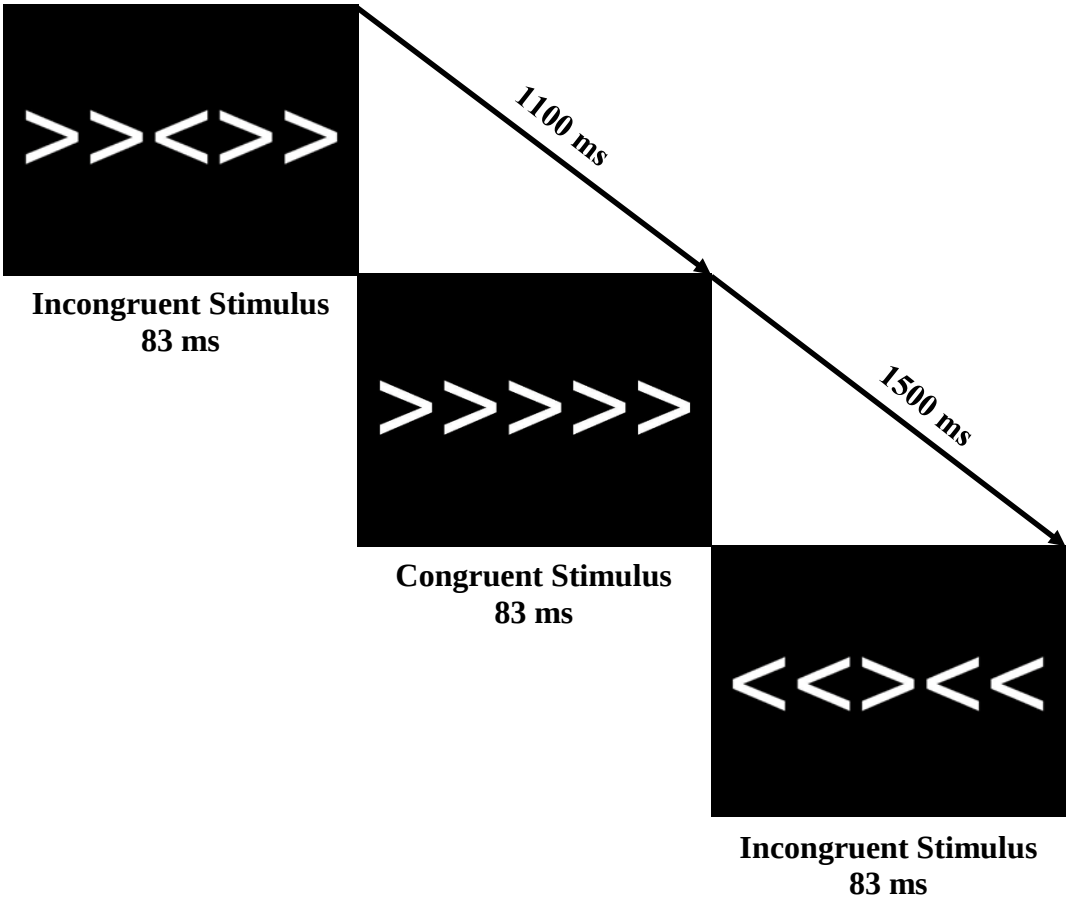
After seven days of wearing the device, all participants returned to the laboratory following an overnight fast of at least 10 hours. Participants were asked to abstain from exercise and caffeine on the day of testing, due to the known effects of caffeine (Brunyé, Mahoney, Lieberman, & Taylor, 2010) and acute exercise (Hillman, Snook, & Jerome, 2003) on cognitive performance. Participants were seated in a sound attenuated testing chamber while they completed a modified version of the Eriksen Flanker task (Eriksen & Eriksen, 1974) to assess attentional inhibition. Participants were given 40 practice trials with the experimenter in the room, and then received 2 blocks of 100 trials in quick succession.

3.3. MEASURES

3.2.1. Flanker Task

To assess attentional inhibition, participants completed a modified version of the Eriksen Flanker task (Eriksen & Eriksen, 1974), presented in Figure 1. Participants were instructed to respond as accurately and quickly as possible to the direction of a centrally presented arrow. Stimuli were presented on a computer screen approximately one meter away from the seated participant and consisted of five 2.5 cm tall white line drawn arrows on a black background. Participants were asked to pay attention to a centrally located target arrow presented amid an array of four task-irrelevant distractor arrows, and press a button using their left thumb when the target arrow faced to the left (e.g., '<'), and their right thumb when the target arrow faced to the right (e.g., '>'). After task instructions were given, participants were afforded time to ask questions and 40 practice trails were administered. Then two experimental blocks of 100 trials were presented using Neuroscan Stim software (Compumedics, Charlotte, NC). Each block consisted of 50 congruent (e.g., <<<<< or >>>>>) and 50 incongruent (e.g., <<><< or >><>>) trials randomly ordered throughout the block. Stimuli were presented for 83ms, with an

equiprobable jittered inter-stimulus interval of either 1100, 1300, or 1500ms. Behavioral performance indices of interest included congruent and incongruent accuracy (measured as % correct) as well as mean response time for correct trials.



Note: Figure 1. Attentional Inhibition was measured using a Modified version of the Eriksen Flanker task. Congruent or incongruent stimuli were presented for 83 milliseconds (ms), with an equiprobable jittered inter-stimulus interval of either 1100, 1300, or 1500ms.

3.3.2. Anthropometrics and Adiposity Assessment

Body mass index (BMI, kg/m^2) was calculated using standing height and weight measurements, completed using a stadiometer (model 240; SECA, Hamburg, Germany) and a digital scale (WB-300 Plus; Tanita, Tokyo, Japan) respectively. Participants were measured without shoes, while wearing only light clothing. The average of 3 measurements of height and

weight were used for analyses. Adipose tissue was measured by DXA using a Hologic QDR 4500A bone densitometer (Software version 13.4.2; Hologic, Bedford, Ma). The standard Hologic software was used to assess whole body % fat (%Fat), as previously described (Khan et al., 2015).

3.3.3. Physical Activity Assessment

All participants received an accelerometer (model wGT3X-BT, firmware 1.8.0; ActiGraph, Pensacola, Florida) and were instructed on proper wear. Participants were asked to wear the device for at least seven consecutive days over their right hip during waking hours and to remove for bathing, swimming, and sleeping. Daily physical activity levels were calculated using Actilife software (software version 6.13.3; ActiGraph). The Troiano (2007) algorithm was used to validate wear time, and participants were excluded from analyses if they did not wear the accelerometer at least 480 minutes per day, for a minimum of four out of seven wear days. Freedson (1998) cut points were used to categorize physical activity intensity. The % of time in moderate to vigorous physical activity (%MVPA) was defined as the % of time spent engaging in moderate or greater levels of physical activity (1,952 counts per minute or higher) out of the total wear time.

3.4. STATISTICAL ANALYSIS

Data were analyzed using SPSS (SPSS v. 24, Chicago, Illinois) with α threshold of $P = 0.05$. Statistical analysis first involved conducting bivariate correlations using Pearson product-moment correlation coefficients between demographics (e.g., age, sex, income level), activity, IQ, adiposity, and behavioral performance measures within task congruency (accuracy and reaction time). Pearson correlation analyses were conducted to determine the demographic

variables which were related to attentional inhibition, and to control for them as possible confounds in subsequent regression analyses.

Hierarchical linear regression models were developed to determine the contribution of %MVPA and %Fat above any important demographic variables established by bivariate analyses. Thus, step one consisted of the demographic variables that correlated with measures of Flanker task performance, adiposity, or physical activity. The second and final step in the regression analysis consisted of both %MVPA and %Fat, plus covariates. Analyses were also conducted examining the interaction of %Fat and %MVPA (%MVPA * (1/%Fat)) to assess the extent to which activity and adiposity may simultaneously affect attentional inhibition. To test the influence of any interaction effect, participants were bifurcated based on the median value for %MVPA and %Fat. Subsequent group differences were assessed using an independent samples *t*-test.

CHAPTER 4: STUDY 1 RESULTS

4.1. PARTICIPANT DEMOGRAPHICS

All of the collected participant characteristics decomposed by gender are presented in Table 2.

Table 2

Demographic Information for All Participants and All Participants Categorized by Sex

Variable	All Participants *M (SEM)*	Females *M (SEM)*	Males *M (SEM)*
Sample size (*n*)	65	39	26
Age (years)	34.08 (0.67)	35.41 (0.80)	32.08 (1.08)
Income (*n* (%))			
Low, $0-$29,999	18 (27.7)	9 (23.0)	9 (34.6)
Medium, $30,000-$69,999	23 (35.4)	15 (38.5)	8 (30.8)
High, $70,000+	24 (36.9)	15 (38.5)	9 (34.6)
IQ (K-BIT2 composite)	109.48 (1.57)	108.36 (1.84)	111.08 (2.80)
BMI (kg/m^2)	30.70 (0.77)	32.43 (1.09)	28.10 (0.80)
Obese "BMI $\geq$30kg/m^2" (*n* (%))	31 (47.7)	25 (64.1)	6 (23.1)
Fat (%)	35.89 (1.17)	41.38 (1.11)	27.65 (1.20)
MVPA (%)	4.75 (0.36)	3.91 (0.41)	6.02 (0.58)

4.2. BIVARIATE CORRELATIONS

Preliminary bivariate correlations between Flanker task performance and demographic variables were conducted to determine the demographic variables which were related to

attentional inhibition, and to control for them as possible confounds in subsequent regression analyses. Bivariate correlations revealed a significant positive relationship between IQ and task accuracy during the congruent condition of the Flanker task. In the incongruent condition of the Flanker task, task accuracy was positively related to %MVPA (r = 0.30, P = 0.02), and negatively associated with %Fat (r = -0.26, P = 0.04). However, there were no significant relationships between mean task response time and demographic variables (all P's > 0.13). Additionally, a negative relationship existed between %MVPA and %Fat (r = -0.45, $P \leq 0.01$). Furthermore, age was significantly and positively correlated with %Fat (r = 0.37, $P \leq 0.01$), and negatively associated with %MVPA (r = -0.38, $P \leq 0.01$). A negative association between sex (Female = 0, Male = 1) and %Fat (r = -0.72, $P \leq 0.01$) along with a positive relationship with %MVPA (r = 0.36, $P \leq 0.01$), indicated that female participants had a higher %Fat and engaged in less %MVPA than male participants. Income was not related to task performance (all P's > 0.14). Demographic variables that were significantly correlated with behavioral performance, adiposity, or physical activity were included in the first step of regression analysis. All of the initial bivariate correlation results are presented in Table 3.

Table 3

Correlations Between Measures of Attentional Inhibition and Demographic Variables

Variable	Age	Sex	Income	IQ	%Fat	%MVPA
Congruent Accuracy	0.02	0.18	0.13	0.41*	-0.24	0.21
Congruent Mean RT	0.12	-0.13	0.04	-0.12	0.13	-0.03
Incongruent Accuracy	0.05	0.12	0.02	0.09	-0.26*	0.30*
Incongruent Mean RT	0.18	-0.18	0.10	-0.12	0.19	-0.07
%Fat	0.37*	-0.72**	0.09	0.02	-	-0.45**
%MVPA	-0.38**	0.36**	-0.18	-0.14	-0.45**	-

Note: * P < 0.05 (2-tailed), **P < 0.01 (2-tailed), RT = Response Time

4.3. HIERARCHICAL LINEAR REGRESSION ANALYSIS

Hierarchical linear regression models were developed to determine the contribution of %MVPA and %Fat above any important demographic variables established by bivariate analyses. Linear regression analysis revealed that IQ was the only significant positive predictor of accuracy during the congruent condition in Step 1. However, the addition of %MVPA and %Fat in Step two significantly improved the model for the accuracy in congruent and incongruent conditions. Step two revealed a significant positive effect of %MVPA, whereas the more time spent in MVPA related to higher accuracy performance for incongruent accuracy.

Although, IQ was the only significant predictor of accuracy in the congruent condition, the inclusion of %MVPA revealed a marginal, but non-significant, positive trend for the congruent Flanker condition. Additionally, the inclusion of %Fat in Step two revealed a marginal negative trend in the incongruent condition of the Flanker task.

There were no significant models for the prediction of reaction time in either condition. The addition of an interaction term in step two did not significantly improve the model for accuracy in the congruent condition. In contrast, during the incongruent condition, the addition of an interaction term significantly improved the model, and was a significant positive predictor of accuracy. Results of hierarchical linear regression analysis with measures of attentional inhibition as the dependent variable are presented in Table 4.

Table 4

Summary of Hierarchical Regression Analysis for Flanker Task Accuracy

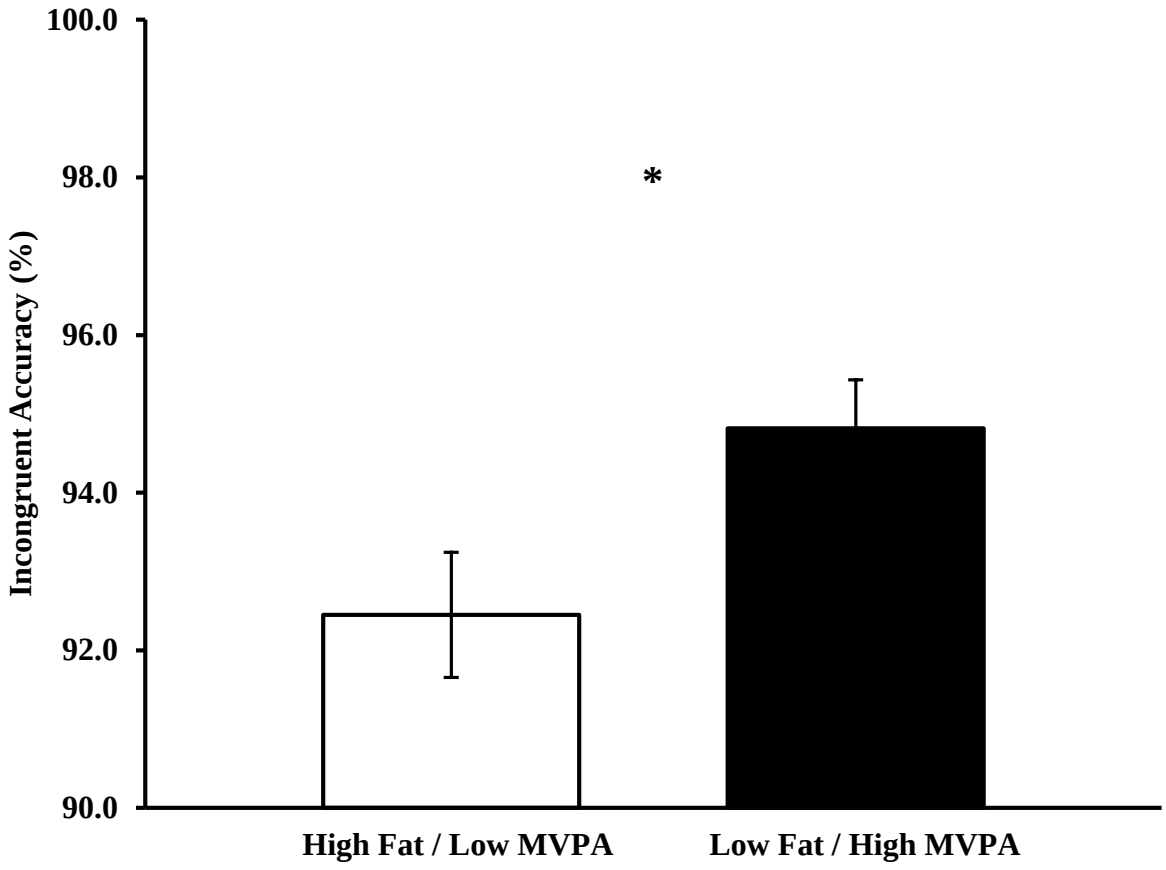
	Congruent Accuracy			Incongruent Accuracy		
Step and Variable	β	ΔR^2	Model *p*	β	ΔR^2	Model *p*
Step 1		0.19*	0.01		0.02	0.69
Age	0.01			0.08		
Sex	0.14			0.12		
IQ	0.40*			0.06		
Step 2		0.09*	< 0.01		0.15*	0.04
%Fat	-0.25			-0.34†		
%MVPA	0.23†			0.31*		
Step 2						
Interaction term	0.26†	0.04†	< 0.01	0.45*	0.12*	0.04

Note: * P < 0.05 (2-tailed), † P < 0.10 (2-tailed)

4.4. INDEPENDENT SAMPLES T-TEST

To illustrate this interaction effect, participants were bifurcated based on the median %MVPA (Median = 4.13%) and %Fat (Median = 36.13%). Participants were then categorized into four groups, based on the %MVPA and %Fat classification they fell into (i.e., participants

who were above the median in %MVPA and above the median in %Fat would be characterized as High %MVPA/High %Fat). Subsequent group differences were assessed using an independent samples *t*-test. Relative to the individuals categorized as Low %MVPA/High %Fat, individuals in the High %MVPA/Low %Fat category had significantly higher performance on the incongruent condition ($t(43) = -2.42$, $P = 0.02$), presented in Figure 2.



Note: Figure 2. Incongruent Flanker task response accuracy data as a function of physical activity/adiposity grouping. Error bars indicate standard error of the mean. * indicates significance at $P < .05$.

CHAPTER 5: STUDY 2 METHODOLOGY

5.1. PARTICIPANTS

Participants were recruited from the east-central region of Illinois and provided written informed consent in accordance with the University of Illinois Institutional Review Board. Participants were recruited from two on-going trials (The Human Gut-Microbiota-Brain Project and Investigating the Effects of Avocado Intake on Metabolism and Cognition: A Systems Approach (NCT02740439)) at baseline. To qualify, all participants reported being free of neurological, metabolic, and gastrointestinal disease (i.e. Cardiovascular disease, ADHD) and reported no current use of anti-psychotic or anti-anxiety medication. In total, 97 adult subjects between the ages of 25-45 years participated in the study. Participants were excluded if they had a history of neurological disease, use of anti-psychotic or anti-anxiety medication, or any chronic metabolic diseases. Intelligence quotient (IQ) was evaluated using the Kaufman Brief Intelligence Test 2 (K-BIT2). Table 5 lists participants' inclusion-exclusion criteria. Briefly, participants were excluded from analysis for incomplete body composition (n=2) or habitual physical activity data (n=10), if they were outliers on measures of cognitive control (n=6), or electroencephalographic (EEG) data had excessive noise (n=9). Therefore, analyses were conducted on a final sample of 70 subjects (29 males, 41 females).

Table 5

Inclusion-Exclusion Criteria for Participants

Inclusion	Exclusion
1. 25-45 years of age	Below 25 or above 45 years of age
2. No history of neurological, metabolic or gastrointestinal disease	Any reported neurological, metabolic or gastrointestinal disease
3. Complete body composition scan	Unable to complete DXA scan
4. Wear habitual physical activity monitor	Insufficient wear time of the accelerometer (minimum 480 minutes per day for 4 out of 7 possible wear days)
5. Perform cognitive tasks within ± 3 *SD* of the mean for accuracy in all task conditions	Performance below 85% accuracy in any cognitive task or task condition
6. Clean EEG data	Visual inspection revealed drift, incomplete data, or excessive noise in EEG data

5.2. PROCEDURES

Participants underwent two testing sessions. On the first day of testing, participants provided informed consent and were screened using a medical history and demographic questionnaire. Following screening, intelligence quotient (IQ) was evaluated using the Kaufman Brief Intelligence Test 2 (K-BIT2) based on the age-normed standardized IQ exam administered by trained experimenters. Participants were categorized into three levels of socioeconomic status (SES) (Low: $0-$29,999; Middle: $30,000-$69,000; High: >$70,000) based on their total household income, utilizing the demographic questionnaire. Next, participants completed a whole body DXA scan to assess adiposity, and height and weight were assessed using a stadiometer (model 240; SECA, Hamburg, Germany) and a digital scale (WB-300 Plus; Tanita, Tokyo, Japan) respectively. At the conclusion of testing session one, participants were provided with an accelerometer and instructed on proper wear procedures.

After a minimum of seven days, participants returned to the laboratory following an overnight fast of at least 10 hours. Participants were asked to abstain from exercise and caffeine on the day of testing, due to the known effects of caffeine (Brunyé et al., 2010) and acute exercise (Hillman, Snook, & Jerome, 2003) on cognitive performance. Participants were fitted with a 64 channel cap (SynAmps2 64 Channel Quik-Cap, Neuroscan) and seated in a sound attenuated chamber while they completed a modified version of the Eriksen Flanker task (Eriksen & Eriksen, 1974) to assess attentional inhibition. Participants were given 40 practice trials with the experimenter in the room, and then received 2 blocks of 100 trials in quick succession.

5.3. MEASURES

5.3.1. Flanker Task

To assess attentional inhibition, participants completed a modified version of the Eriksen Flanker task (Eriksen & Eriksen, 1974) in which they were instructed to respond as accurately and quickly as possible to the direction of a centrally presented arrow. Stimuli were presented on a computer screen approximately one meter away from the seated participant and consisted of five 2.5cm tall white line drawn arrows on a black background. Participants were asked to pay attention to a centrally located target arrow presented amid an array of four task-irrelevant distractor arrows flanking the target on both sides. After task instructions, participants were afforded time to ask questions and 40 practice trails were administered. Then two experimental blocks of 100 trials were presented using Neuroscan Stim software (Compumedics, Charlotte, NC). Each block consisted of 50 congruent (e.g., <<<<< or >>>>>) and 50 incongruent (e.g., <<><< or >><>>) trials randomly ordered throughout the block. Stimuli were presented for 83ms, with an equiprobable jittered inter-stimulus interval of either 1100, 1300, or 1500ms.

5.3.2. Anthropometrics and Adiposity Assessment

Body mass index (BMI, kg/m^2) was calculated using standing height and weight measurements, completed using a stadiometer (model 240; SECA, Hamburg, Germany) and a digital scale (WB-300 Plus; Tanita, Tokyo, Japan) respectively. Participants were measured without shoes, while wearing only light clothing. The average of 3 measurements of height and weight were used for analyses. Adipose tissue was measured by DXA using a Hologic QDR 4500A bone densitometer (Software version 13.4.2; Hologic, Bedford, Ma). The standard Hologic software was used to assess whole body % fat (%Fat).

5.3.3. Physical Activity Assessment

Participants received an accelerometer (model wGT3X-BT, firmware 1.8.0; ActiGraph, Pensacola, Florida) and were instructed on proper wear. Participants were asked to wear the device for at least seven consecutive days over their right hip during waking hours and only remove it for bathing, swimming, and sleeping. Daily physical activity levels were calculated using Actilife software (software version 6.13.3; ActiGraph). Habitual physical activity measurements were considered valid if participants wore the accelerometer at least 480 minutes per day for a minimum of four out of seven wear days (Troiano, 2007). Physical activity levels were categorized by Freedson (1998) cut points, with sedentary time defined as the % of time spent engaging in less than 100 counts per minute (roughly equivalent to < 1.5 METS). %MVPA was defined as the % of time spent engaging in moderate or greater levels of physical activity (1,952 counts per minute or higher) out of the total wear time.

5.3.4. Electroencephalogram (EEG) Recording

EEG activity was recorded from 64 electrode sites via a Neuro-scan Quik-cap (Compumedics, Charlotte, NC), with scalp electrodes arranged in the international 10-10 system

(Chatrian, Lettich, & Nelson, 1985). A midline sensor placed between Cz and CPz served as a reference and AFz served as the ground. Using a Neuroscan Synamps2 amplifier, continuous EEG signal was digitized at a sampling rate of 500 Hz, amplified 500 times to 70-Hz filter with a direct current and a 60-Hz notch filter. To account for eye movement and blinks, four additional electrodes were placed at the outer canthus of each eye and above and below the left orbit and electro-oculographic (EOG) activity was recorded. Impedance values for all electrodes were ≤10 k ohms.

Offline using ERPLAB (Lopez-Calderon & Luck, 2014), recordings were referenced to averaged mastoids (M1, M2). Data underwent an independent components analysis (ICA) to systematically reject artifacts caused by eye blinks. Trials were rejected if a response error occurred or if a component identified during the ICA correlated at or above 0.35 with the vertical EOG channel. Data was subjected to a 30 Hz low pass filter before stimulus locked epochs were created for correct trials from -200 to 1000 ms, baseline corrected using the -200 to 0 ms time window. Epochs were excluded if the moving window peak-to-peak amplitude exceeded ±75 μV using a 100 ms window and a 50 ms window step or was ± > 3 *SD* away from the mean. A region of interest (ROI) over the central parietal region (C1, CZ, C2, CP1, CPZ, CP2) was selected based on the electrodes encompassing the topographic maxima from 300-600ms, as determined using a grand average of all correct congruent and incongruent trials of the Flanker task. The P3 component was defined as the largest positive-going peak within a 300–600-ms latency window. ERP variables of interest were the ROI mean P3 amplitude, measured separately for congruent and incongruent stimuli and the ROI mean amplitude difference (incongruent trials – congruent trials). The mean amplitude difference was used to index the ability for upregulation of attentional inhibition following an increase in task demands

5.4. STATISTICAL ANALYSIS

Initial analysis involved bivariate correlations using Pearson product-moment correlation coefficients between demographics (e.g., age, sex, IQ, SES), activity level (%Sedentary, %MVPA), adiposity (%Fat), and behavioral and neuroelectric indices (Flanker accuracy and ROI mean amplitude) of attentional inhibition. All neuroelectric analyses were conducted using the central parietal ROI mean amplitude, specifically the congruent and incongruent mean amplitudes. ROI mean amplitude difference was calculated as incongruent mean amplitude minus congruent mean amplitude and was used as a neuroelectric measure of attentional inhibition upregulation in subsequent analyses. Additional bivariate correlations were conducted between Flanker task accuracy and ROI mean amplitude difference to determine the extent to which ROI mean amplitude difference related to behavioral performance measures.

Hierarchical linear regression analyses were used to determine the contribution of adiposity and different physical activity levels on behavioral and neuroelectric measures of attentional inhibition after controlling for confounding variables. Thus, age, sex, and IQ were included in step one as control variables. To determine the contribution of physical activity and adiposity beyond the demographic variables, %Fat and %MVPA were added to step two of the analysis. Lastly, to determine the influence of sedentary time above and beyond the influence of adiposity and physical activity, the third and final step included %Sedentary. Standardized β weights were used to measure the influence of each predictor on measures of attentional inhibition. Overall model fit was determined through ANOVA F statistic, and R^2 was used to determine the change in variation that was explained following the addition of each predictor variable. To illustrate the effect of sedentary time on attentional inhibition, participants were trifurcated based on %Sedentary. Subsequent group differences were assessed using an ANOVA.

CHAPTER 6: STUDY 2 RESULTS

6.1. PARTICIPANT DEMOGRAPHICS

All of the collected participant characteristics decomposed by gender are presented in Table 6.

Table 6

Demographic Information for All Participants and All Participants Categorized by Sex

Variable	All Participants *M (SEM)*	Females *M (SEM)*	Males *M (SEM)*
Sample size (*n*)	70	41	29
Age (years)	34.66 (0.69)	35.15 (0.82)	32.55 (1.08)
Income (*n* (%))			
Low, $0-$29,999	22 (31.4)	9 (22.0)	13 (44.8)
Medium, $30,000-$69,999	26 (37.2)	17 (41.4)	9 (31.0)
High, $70,000+	22 (31.4)	15 (36.6)	7 (24.2)
IQ (K-BIT2 composite)	109.93 (1.75)	107.44 (1.80)	113.42 (3.32)
BMI (kg/m^2)	30.63 (0.78)	32.80 (1.06)	27.56 (0.87)
Obese "BMI $\geq$30kg/m^2" (*n* (%))	31 (44.3)	26 (63.4)	5 (17.2)
Fat (%)	35.53 (1.21)	42.12 (0.96)	26.23 (1.26)
Sedentary (%)	64.99 (0.90)	65.05 (1.40)	64.91 (0.92)
MVPA (%)	4.80 (0.34)	3.80 (0.37)	6.22 (0.52)

6.2. BIVARIATE CORRELATIONS

Preliminary bivariate correlations between Flanker task performance (behavioral and neuroelectric) and demographic variables were conducted to determine the demographic variables which were related to attentional inhibition, and to control for them as possible

confounds in subsequent regression analyses. Pearson product-moment correlations revealed a positive correlation between age and both congruent (r = 0.26, P = 0.03) and incongruent (r = 0.29, P = 0.02) response time for the Flanker task. Age also exhibited a positive relationship with P3 ROI mean amplitude, but only for the congruent trials (r = 0.32, P = 0.01). Additionally, there was a negative relationship between age and both ROI mean amplitude difference (r = -0.30, P = 0.01) and %MVPA (r = -0.38, $P \leq 0.01$), whereby younger adults exhibited greater ability to upregulate between the task conditions. There was a positive association between sex and congruent (r = 0.25, P = 0.04) response accuracy, indicating that male participants correctly responded at a higher rate than females. Likewise, sex was positively associated with %MVPA (r = 0.43, $P \leq 0.01$), indicating that male participants spent more time engaging in moderate to vigorous physical activity than their female counterparts. In addition, IQ was positively related to congruent (r = 0.38, $P \leq 0.01$) task accuracy, while %Fat was inversely correlated to congruent (r = -0.27, P = 0.03) task accuracy. %Fat was also negatively associated with incongruent task accuracy (r = -0.30, P = 0.01) and was positively correlated to P3 ROI mean amplitude in congruent trials (r = 0.24, P = 0.04). Bivariate correlations indicated that %Sedentary was not related to any demographic variable of interest (all P's > 0.19). Demographic variables that were significantly correlated with task performance, adiposity, or physical activity were included in the first step of regression analysis.

Initial bivariate correlation analyses were conducted between behavioral and neuroelectric measures of Flanker task performance, to determine the extent of which ROI mean amplitude was related to behavioral performance measures. Congruent response time was related to both congruent (r = -0.29, P = 0.01) and incongruent (r = -0.24, P = 0.04) P3 ROI mean amplitude, while congruent accuracy was related to incongruent P3 ROI mean amplitude (r =

0.27, $P = 0.03$). Interestingly, results revealed a significant positive relationship between P3 ROI mean amplitude difference and all measures of Flanker task accuracy (congruent $r = 0.27$, $P = 0.03$; incongruent $r = 0.34$, $P \leq 0.01$). Bivariate correlation results between behavioral and neuroelectric measures of Flanker task performance are presented in Table 7.

Table 7

Correlations Between Behavioral Task Performance and Neuroelectric Measures of Attentional Inhibition

Variable	Congruent P3 Mean Amplitude	Incongruent P3 Mean Amplitude	Mean Amplitude Difference
Congruent Accuracy	0.15	0.27*	0.27*
Congruent Mean Response Time	-0.29*	-0.24*	0.07
Incongruent Accuracy	-0.12	0.04	0.34**
Incongruent Mean Response	-0.19	-0.20	-0.04

Note: * $P < 0.05$ (2-tailed), ** $P < 0.01$ (2-tailed)

6.3. HIERARCHICAL LINEAR REGRESSION ANALYSIS

6.3.1. Behavioral Task Performance

Demographic variables significantly correlated with behavioral measures of Flanker task performance (i.e. age, sex, and IQ) were adjusted for in Step one. Step one of the model was significant for the congruent ($F = 4.72$, $P = 0.01$) condition of Flanker, with IQ being a positive predictor of congruent ($\beta = 0.34$, $P \leq 0.01$) task accuracy. Step one of the model for the incongruent ($F = 1.51$, $P = 0.22$) condition failed to reach significance. Step two of the model was significant for both congruent ($F = 3.39$, $\Delta R^2 = 0.09$, $P = 0.01$) and incongruent ($F = 2.56$, $\Delta R^2 = 0.15$, $P = 0.04$) task accuracy. IQ was the only positive predictor of congruent ($\beta = 0.36$, $P \leq 0.01$) task accuracy, however %Fat ($\beta = -0.35$, $P = 0.08$) and %MVPA ($\beta = 0.24$, $P = 0.08$)

were trending predictors of incongruent task accuracy. The addition of %Fat and %MVPA did not significantly improve the model in the congruent (ΔR^2 = 0.03, P = 0.27) condition, however the addition did significantly improve the incongruent (ΔR^2 = 0.10, P = 0.03) accuracy model. Step three of the model was significant for both conditions of Flanker task accuracy (congruent F = 2.80, P = 0.02; incongruent F = 2.27, P = 0.05), however the addition of %Sedentary did not improve the model for either condition (congruent ΔR^2 = 0.00, β = 0.04, P = 0.76; incongruent ΔR^2 = 0.01, β = -0.12, P = 0.35).

Results of the hierarchical linear regression for Flanker response time are described herein, with significant demographic variables adjusted for in Step one, %Fat and %MVPA included in Step two, and finally %Sedentary in Step three. In the congruent condition of the Flanker task, neither Step one (F = 2.10, P = 0.11), Step two (F = 1.46, P = 0.22), nor Step three (F = 1.24, P = 0.30) of the model were significant. Similarly, in the incongruent condition, neither Step one (F = 2.25, P = 0.09), Step two (F = 1.68, P = 0.15), nor Step three (F= 1.38, P = 0.24) of the model were significant.

6.3.2. Regression Models for the P3 ERP Component

Hierarchical linear regression analyses were performed on congruent and incongruent ROI mean amplitudes (see Table 8). Step one of the model was significant for congruent (F = 3.06, P = 0.03), but not incongruent (F = 1.68, P = 0.18) ROI mean amplitude, with age (β = 0.31, P = 0.01) as a significant positive predictor of congruent ROI mean amplitude. The addition of %MVPA and %Fat did not significantly improve the model for either the congruent (ΔR^2 = 0.02, P = 0.43) or incongruent (ΔR^2 = 0.03, P = 0.35) ROI mean amplitude, as Step two failed to reach significance in either condition (congruent F = 2.17, P = 0.07; incongruent F = 1.43, P = 0.22).

Similarly, Step three of the model failed to reach significance for both the congruent (F = 1.87, P = 0.10) and incongruent (F= 1.25, P = 0.30) ROI mean amplitudes.

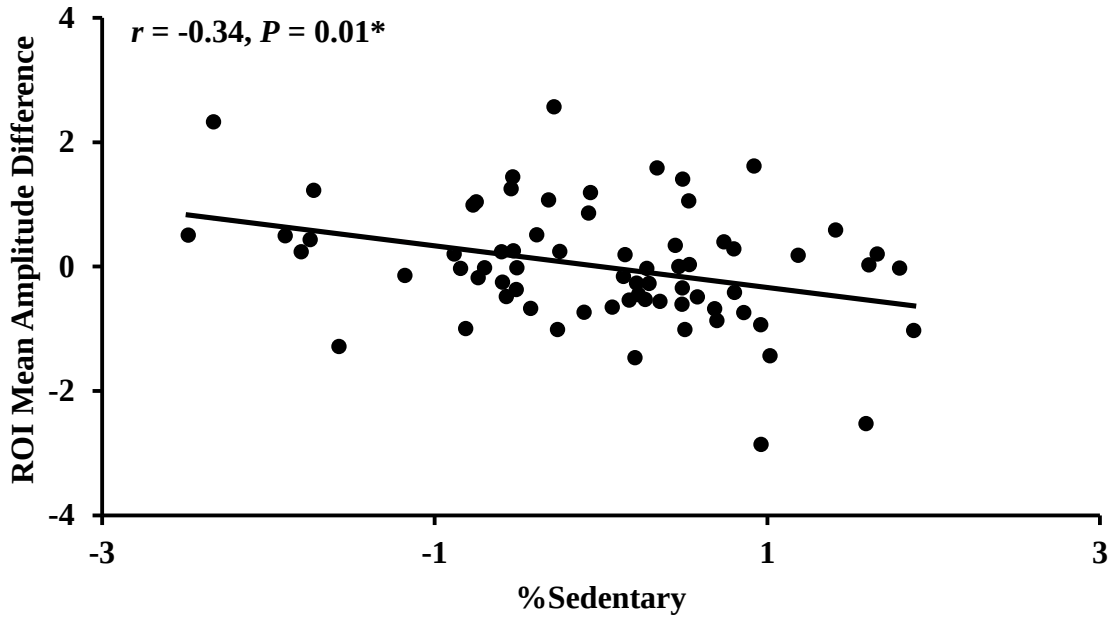
To assess the relationship between %Sedentary and ROI mean amplitude difference, an additional hierarchical linear regression analysis was performed. Step one of the model was significant (F = 3.51, P = 0.02), as age (β = -0.26, P = 0.04) was a negative predictor of ROI mean amplitude difference. The addition of %Fat and %MVPA in Step two did not significantly improve the model (ΔR^2 = 0.01, P = 0.81), with Step two no longer significant (F = 2.14, P = 0.07). However, Step three of the model reached significance (F = 3.30, P = 0.01), as the addition of %Sedentary significantly improved the model (ΔR^2 = 0.10, P = 0.01). Interestingly, the addition of %Sedentary (β = -0.35, P = 0.01) showed a negative association with ROI mean amplitude difference, such that those who spent a higher percentage of their time being sedentary had smaller ROI mean differential amplitudes. There were no significant relationships with P3 latency. Results of hierarchical linear regression are presented in Table 8 and Figure 3.

Table 8

Summary of Hierarchical Regression Analysis for Flanker Task Accuracy

Step and Variable	Congruent P3 Mean Amplitude			Incongruent P3 Mean Amplitude			Mean Amplitude Difference		
	β	ΔR^2	Model p	β	ΔR^2	Model p	β	ΔR^2	Model p
Step 1		0.12*	0.03*		0.07	0.18		0.14*	0.02*
Age	0.31*			0.18			-0.26*		
Sex	-0.06			-0.01			0.10		
IQ	0.13			0.21†			0.18		
Step 2		0.02	0.07†		0.03	0.22		0.01	0.07†
%Fat	0.20			0.25			0.13		
%MVPA	-0.09			-0.08			0.01		
Step 3		0.01	0.10		0.01	0.30		0.10*	0.01*
%Sedentary	0.09			-0.08			-0.35*		

Note: * P < 0.05 (2-tailed), ** P < 0.01 (2-tailed)

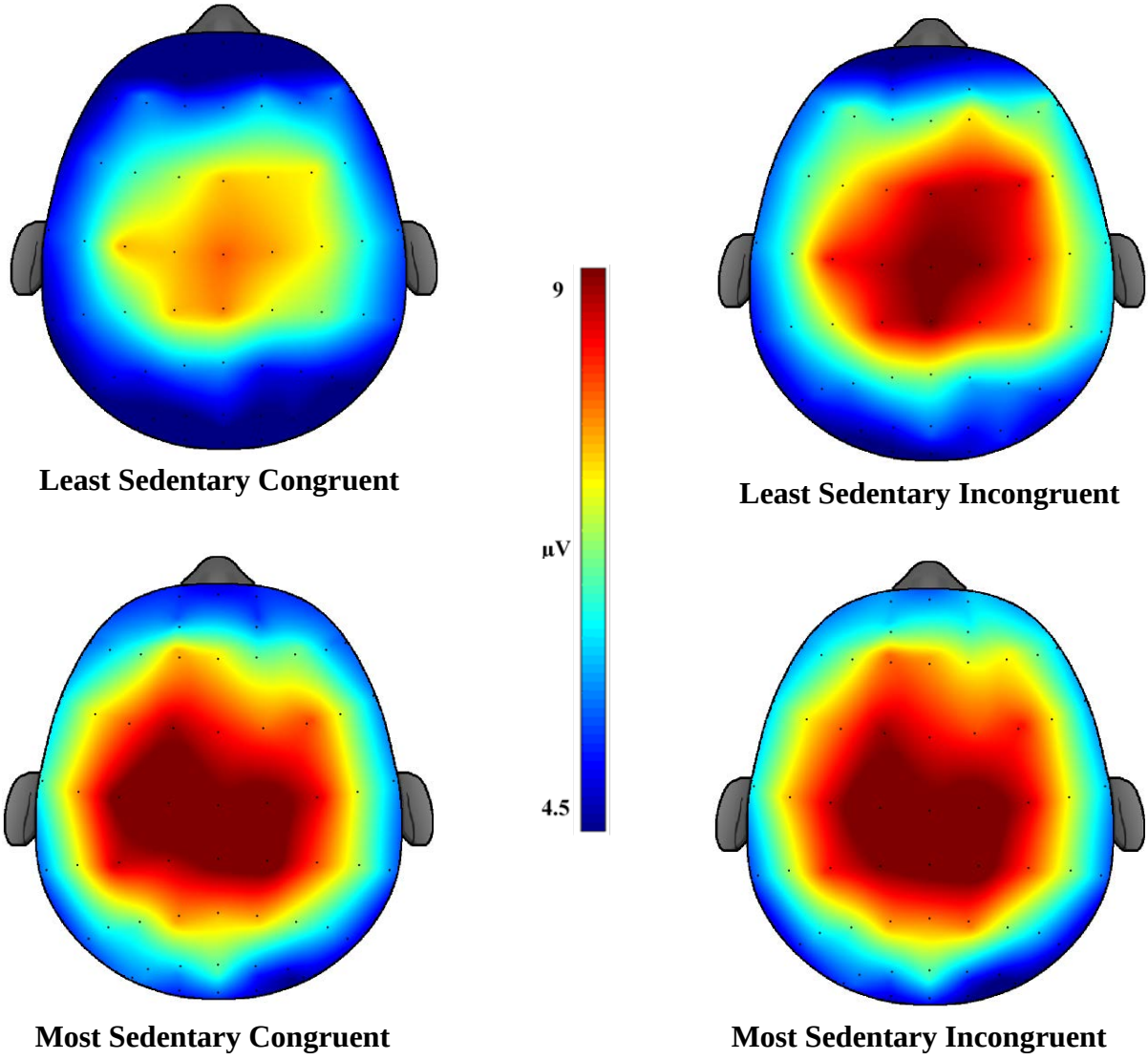


Note: Figure 3. Partial regression plot (*n*=70) depicting the relationship between %Sedentary and ROI Mean amplitude difference after controlling for significant demographic variables, %Fat, and %MVPA. Axis depict *Z* score, * indicates significance at $P < .05$.

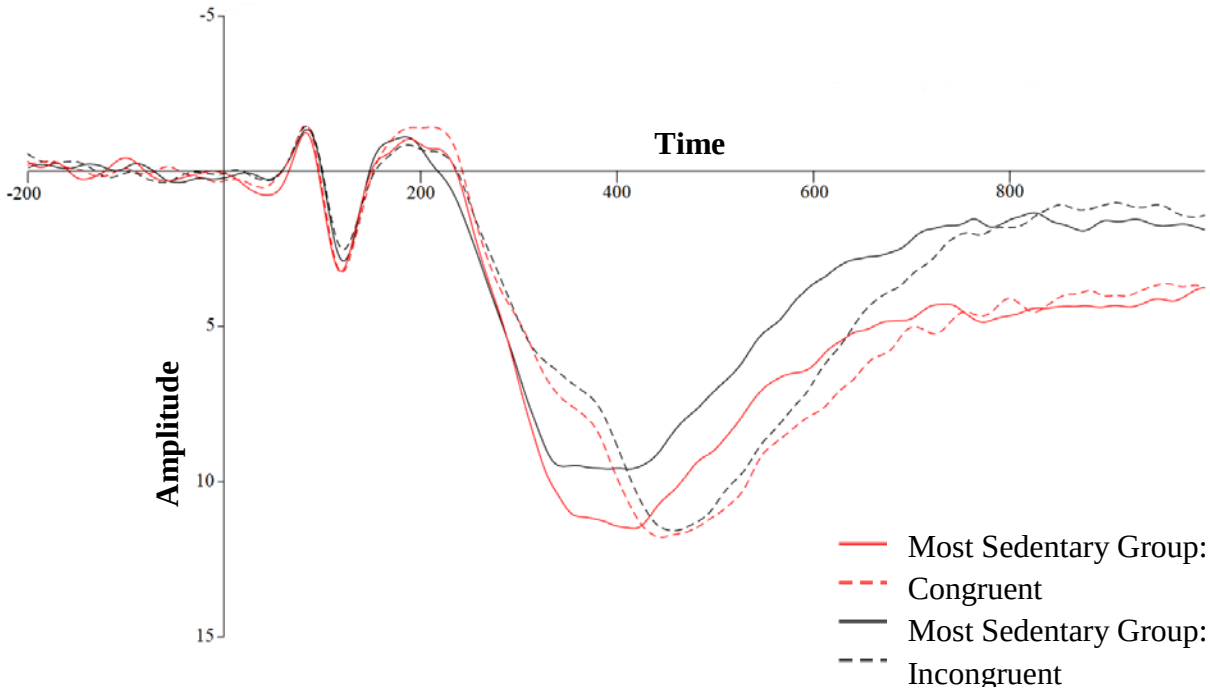
6.4. ANOVA ANALYSIS

A one-way ANOVA was conducted to illustrate the influence of sedentary time on mean amplitude (see Figure 5). Participants were trifurcated ($n = 23$) based on %Sedentary. There was a significant effect %Sedentary on ROI mean amplitude difference ($F = 3.66$, $P = 0.03$) and a marginally significant effect on congruent ROI mean amplitude ($F = 2.97$, $P = 0.06$). Subsequent group comparisons revealed that the ROI mean amplitude difference of the individuals who spent the highest percentage of time sedentary ($M = 0.04$, $S.E = 0.37$) was significantly lower than the mean of the least sedentary ($M = 1.16$, $S.E. = 0.31$). Additionally, although marginally significant ($P = 0.07$), those who were the least sedentary ($M = 7.63$, $S. E. = 0.56$) trended

towards showing a lower congruent ROI mean amplitude compared to those participants who spent the most time being sedentary (M = 9.30, $S.E.$ = 0.60), presented in Figures 4 and 5.



Note: Figure 4. Grand-average topographic plots for P3 mean amplitude (300-600 ms) for congruent (left) and incongruent (right) Flanker conditions among the least and most sedentary individuals. Participants were trifurcated (n = 23 per group) based on %Sedentary.



Note: Figure 5. Grand average event-related brain potential waveforms illustrating P3 mean amplitude for congruent and incongruent Flanker conditions among the least and most sedentary individuals Participants were trifurcated (n = 23 per group) based on %Sedentary.

CHAPTER 7: DISCUSSION

In the present study, the relationship between physical activity, adiposity, sedentary time, and attentional inhibition were investigated using neuroelectric and task performance measures. Overall, the findings revealed that physical activity has a positive influence on attentional inhibition, after accounting for adiposity demographic variables. Additionally, adiposity is negatively related to attentional inhibition, but that effect is not present after accounting for related variables. Furthermore, an interaction effect was observed for both physical activity and adiposity, indicating there is an overlapping influence of physical activity and adiposity on attentional inhibition. Finally, time spent being sedentary was negatively related to neuroelectric indices of attentional inhibition, after adjusting for associated variables. More precisely, time spent being sedentary was inversely related to the ability to modulate attentional resources as task demands increased. Modulation of attentional resources is of relevance due to the observed positive relationship between task performance and ROI mean amplitude difference. These findings provide support for the need to increase physical activity and decrease sedentary time in order to maximize attentional inhibition.

7.1. STUDY 1

The goal of study 1 was to explore the relationship between daily physical activity, adiposity, and attentional inhibition in a sample of young to middle-aged adults. Since physical activity and obesity are often related, it was important to examine the contributions of each in conjunction with the other. Consistent with previous work, both age and sex were significantly associated with adiposity (Camhi et al., 2010; Kyle et al., 2001) and %MVPA (Troiano et al., 2008). Furthermore, these data replicate previously observed inverse relationships between

adiposity and cognitive control (Nguyen et al., 2014; Smith et al., 2011), as indicated by negative correlations between %Fat and incongruent Flanker task accuracy. These results show that those participants with more adipose tissue exhibited poorer performance in attentional inhibition, and thus, increased adipose tissue may be detrimental to cognitive performance. Further, after controlling for demographic variables, results showed that %Fat was trending as a negative predictor of attentional inhibition, as measured by incongruent Flanker accuracy. More work is needed to elucidate the relationship between adiposity and attentional inhibition.

Consistent with our a priori hypothesis, these results extend the literature by illustrating a positive contribution of %MVPA to the variance in attentional inhibition, following adjustment of adiposity. Specifically, results showed that after controlling for demographic variables and %Fat, %MVPA persisted as a positive predictor of attentional inhibition in the incongruent condition. Thus, participants who engaged in greater amounts of physical activity were better able to upregulate their attentional inhibition when task demands increased. These findings are consistent with previous research studies, which have discovered that participants who engage in greater amounts of MVPA perform better on tests of cognitive control (Booth et al., 2013; Kerr et al., 2013). This positive influence of physical activity has been demonstrated in older adults as well, with participants who spent more time in MVPA exhibiting greater hippocampal volume (Erickson et al., 2009). However, these aforementioned studies did not directly assess the influence of physical activity after adjusting for the influence of adiposity and other key health behaviors. These results indicate that physical activity has a positive relationship with attentional inhibition, providing evidence for the benefits of increased physical activity in daily life.

Interestingly, an interaction effect was observed for both %MVPA and %Fat whereby individuals who were less active and had greater adiposity exhibited the poorest performance.

Therefore, there is an overlapping influence of physical activity and adiposity on attentional inhibition. Both the positive and negative influences of activity and adiposity, respectively, are related to attentional inhibition. Therefore, even those participants who were the most active experienced the negative effects of higher adipose tissue.

Herein, we demonstrated that both adipose tissue and MVPA influence inhibitory control after accounting for other known confounds. Although physical activity and adiposity are often interrelated, to our knowledge, few studies have examined the combined influence of these health factors on cognitive function, with little consistency across studies (Chang et al., 2016). The present study provides evidence for an overlapping model, wherein physical activity and adiposity jointly affect cognitive function. These results were supported by regression modelling, illustrating that the observed positive relationship between physical activity and attentional inhibition was present both before and after controlling for the effects of adiposity. Additional support is found in the observed negative correlation between %Fat and attentional inhibition, and the negative trend shown in the regression modelling. Given that these relationships were evident for the incongruent task condition, and only trending in the congruent task, these results suggest that participants who have spent more time in MVPA exhibit a greater ability to upregulate their attentional inhibition as task demands increase.

7.2. STUDY 2

In a cross-sectional study among healthy, middle aged adults, study 2 investigated the relationship between sedentary time and behavioral and neuroelectric measures of attentional inhibition. Initial bivariate correlations revealed an expected positive relationship between scores on a task measuring attentional inhibition and objective measures of physical activity, with adiposity inversely related to attentional inhibition. These results are consistent with previous

research studies that observed cognitive control is inversely related to adiposity (Gunstad et al., 2007; Nguyen et al., 2014; Smith et al., 2011) and participants who engaged in greater amounts of MVPA performed better on measures of attentional inhibition (Booth et al., 2013; Hillman et al., 2006). However, after controlling for age, sex, and intelligence, we found only a marginally significant influence of %MVPA or %Fat on behavioral or neuroelectric measures of attentional inhibition.

Consistent with *a priori* hypothesis, time spent being sedentary exhibited a negative relationship with neuroelectric indices of attentional inhibition, after adjusting for adiposity and physical activity. Specifically, time spent being sedentary was inversely related to the ability to modulate attentional resources as task demands increased. The ability to upregulate attentional inhibition in the face of increasing task demands was indexed by computing the mean amplitude difference across central-parietal electrodes, reflecting the P3 maxima. The relevance of this index for task performance was evident in the positive correlations observed between ROI amplitude difference and task accuracy. Regression analyses revealed that individuals who engaged in greater sedentary time exhibited significantly smaller changes in P3 amplitude between task conditions. Thus individuals who were more sedentary exhibited comparatively similar neuroelectric patterns regardless of task difficulty. On the other hand, individuals who are less sedentary appeared to flexibly increase attentional resources when faced with greater task demands. Further, these relationships appeared to be independent of the several demographical, behavioral, and physiological factors previously shown to be relevant for attentional inhibition. Of particular importance, these results were independent of the contrasting influence of adiposity as well as moderate-to-vigorous physical activity, thereby providing support for the independent contributions of sedentary time to attentional control.

A converging body of literature has emerged over the past two decades linking behavioral and physiological factors of physical activity and aerobic fitness to aspects of cognitive control. Individuals who are more active and aerobically fit have been shown to exhibit greater ability for cognitive control, assessed by both behavioral and neuroelectric measures (Hillman et al., 2004), and these measures have been shown to be sensitive to aerobic exercise provision as well (Hillman et al., 2003; Huang, Lin, Hung, & Chang, 2014). Indeed, individuals who are aerobically fit and those who engage in greater habitual physical activity often exhibit faster latencies and greater P3 amplitudes during cognitive control tasks, with effects particularly evident during task conditions that place greater demands on cognitive control (Hillman et al., 2004; Hillman, Kramer, Belopolsky, & Smith, 2006). In addition to neuroelectric data, there is compelling evidence from neuroimaging studies that demonstrate higher fitness level is associated with greater cognitive performance and these relationships are mediated by underlying brain structure (Burzynska et al., 2014; Erickson et al., 2009; McAuley, Kramer, & Colcombe, 2004). Given the plethora of studies demonstrating the functional and structural benefits of physical activity on brain and cognition, it would be expected that greater sedentary time would be inversely related to measures of cognitive control. However, to our knowledge, no previous study has directly addressed this question using objectively measured sedentary activity and relating it to behavioral and neuroelectric indices of cognitive control.

Elucidating the role of sedentary behavior on cognitive function is important given the emerging evidence that sedentary behaviors appear to exert negative effects on a variety of metabolic outcomes in a manner that is independent of engagement in MVPA. An individual can meet the recommended 150 min/week of MVPA while concomitantly spending a considerable proportion of their day being sedentary (Craft et al., 2012). For example, recent work on

sedentary behaviors has linked time spent sitting with distinct physiological effects including dyslipidemia and breaking up sedentary time during the day is beneficially associated with mitigating metabolic risk (Bailey & Locke, 2015; Engeroff, Füzéki, Vogt, & Banzer, 2017; Hamilton, Hamilton, & Zderic, 2007). Although the underlying mechanisms of these relationships are unknown, these observational data beg the question whether the deleterious influence of sedentary time extends to aspects of cognitive control that have been previously shown to be related to physical activity behaviors. Findings from the current study are among the first to link sedentary time to poorer patterns of neuroelectric function during an attentional inhibition task. Specifically, individuals who spent a greater proportion of their day being sedentary exhibited a failure to flexibly modulate or adjust their attentional resources between conditions requiring variable amounts of cognitive control. Interestingly, these relationships were only observed at the trend level for MVPA. Therefore, it is possible that time spent being sedentary may represent a behavioral metric that is more sensitive to neuroelectric indices that underlie attentional inhibition among young-to-middle-aged adults.

In contrast to the positive influence of physical activity on brain and cognition, obese weight status has also been linked to poorer performance on cognitive control tasks and accompanied by structural differences in brain structure and function. Elevated weight status has been shown to be related to neurostructural deficits in the prefrontal and orbitofrontal cortices and in the frontal-subcortical activation of cognitive function (Barkin, 2013; Stanek et al., 2013; Stanek et al., 2011). However, unlike the literature on physical activity, comparatively less is known regarding the role of adiposity or excess fat mass on behavioral and neuroelectric indices of attentional inhibition. A handful of studies in children have examined differences in ERP components across weight status categories and demonstrated that children with obesity exhibit

lapses in error monitoring and differential patterns in error-related negativity (Kamijo et al., 2014). Specific to the P3, children with obesity and insulin resistance exhibit longer P3 latencies and lower amplitudes, relative to their healthy weight and obese without insulin resistance counterparts (Tascilar et al., 2011). Among adults, obese individuals showed slower response time, greater number of errors, and diminished P3 amplitude during a Stroop task assessing inhibitory function (Song et al., 2016).

The present study replicated the inverse relationship between attentional inhibition and adiposity, as evidenced by the inverse relationship observed between %Fat and accuracy in the congruent condition. However, this relationship was not sustained following the adjustment of demographic factors and MVPA. Interestingly, although a positive relationship between %Sedentary time and fat mass was observed, only %Sedentary time emerged as an independent predictor for the ability to modulate attentional resources, as evidenced by a lower differential in P3 ROI amplitude among adults with greater sedentary activity. Given the known relationship between sedentary behavior and greater risk for obesity and metabolic dysfunction, it is possible that previously observed negative relationships between obesity and cognitive control are, to some extent, driven by sedentary behavior. Future experimental trials examining changes in sedentary time with or without changes in fat mass are necessary to conclusively delineate these effects.

7.3. LIMITATIONS

Several limitations are worth considering. Given the cross-sectional design, it is not possible to claim that the relationships presented here are causal. To determine the directionality of these relationships, future experimental or intervention trials will be necessary. In addition, we cannot exclude the possibility that other lifestyle factors or genetics may have contributed to the

study findings. As the relevant variables age, sex, and IQ were controlled for, this risk is reduced, but not eliminated. Another limitation of the study was that the sample of adults were predominantly obese (48%), which is higher than the prevalence observed in the general population (36.5%) (Ogden, Carroll, Fryar, & Flegal, 2015). The aforementioned limitations notwithstanding, the present study had several strengths including the objective assessment of physical activity and sedentary behavior. Virtually all previous studies on the topic of sedentary time, and many previous studies on physical activity, have relied on self-report measures. Finally, the adjustment of covariates assessed using high quality techniques including objectively measured MVPA and utilization of DXA to directly assess adiposity, rather than BMI, are additional strengths of the present study and provided stronger evidence for the importance of physical activity for cognitive function, and the independent influence of sedentary time on attentional inhibition.

7.4. CONCLUSIONS

In conclusion, the relationship between of habitual physical activity, adiposity, sedentary behaviors, and cognitive control was examined. The present findings show that habitual physical activity and adiposity appear to have contrasting influences on attentional inhibition. However, the positive influence of greater physical activity on attentional inhibition was particularly evident for performance during the task condition requiring upregulation of attentional inhibition. This relationship was evident following adjustment for important demographic factors including age, sex, and IQ. Furthermore, the overlapping effects of %Fat and %MVPA show that when looked at simultaneously, both variables together predict attentional inhibition performance.

Moreover, results of this study suggest that an overall increase in time spent being sedentary has independent and negative effects on patterns of neurolectric function during an attentional inhibition. Specifically, individuals who spent a greater proportion of their day engaging in sedentary behaviors exhibited poorer ability to modulate attentional resources between trial conditions eliciting variables degrees of attentional inhibition. Indeed, the degree of attentional resource allocation among the more sedentary individuals remained virtually unchanged between task conditions. The fact that these relationships were independent of the influence of demographics, intellectual ability, MVPA, and adiposity, provides additional evidence indicating that sedentary time may serve as a unique risk factor for poorer cognitive function.

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APPENDIX A: INFORMED CONSENT

UNIVERSITY OF ILLINOIS
AT URBANA-CHAMPAIGN

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The Human Gut-Microbiota-Brain Project

Participant Consent Form

Investigators Directing Research:
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Michael De Lisio, PhD
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University of Illinois at Urbana-Champaign

You are invited to participate in a research study that will help us understand the relationship between lifestyle behaviors, gut function, metabolism, and thinking ability/cognitive function. This form is designed to provide you with information about the study. Today is the first of two visits, with each visit lasting about 2.5 hours. If you agree to be a part of this research, you will complete an exercise test, have your body composition measured using a Dual-Energy X-ray Absorptiometry (DXA), record your diet and fluid intake, wear a physical activity monitor, perform cognitive tasks, collect a fecal and urine sample, and have a small amount of blood drawn. Before we can collect any data, it's important to confirm that you:

1. Are informed about the procedure
2. Give your consent voluntarily (i.e., participate because you want to)
3. Know that you can withdraw your consent at any time
4. Are between 18-44 years old

To make an informed decision, the nature of the procedure and the potential risks and/or benefits are provided below.

What You Will Do in the Experiment:

Today (Day 1)

First we will ask you to complete several questionnaires and measure your height and weight to assess whether you qualify to be part of this study. The questionnaires contain questions pertaining to your ability for vigorous physical activity and previous health history. Based on the information collected you will be verbally informed immediately whether or not you qualify for the study. If you do not qualify for this study, we will not retain any of your information and you will not receive any compensation.

If you qualify for the study, you will also be asked to answer questions about your regular sleep habits and you will undergo a pencil and paper logic and reasoning test. After completing the questionnaire, your eye health will be assessed using a macular densitometer. During this test we will ask you to look into a scope for a few minutes and observe and respond to a flickering blue light. You will be asked to look into a scope (optical coherence tomography) while an image or scan is

taken of your eyes. Your vision will also be tested using letter charts. After the eye tests, you will be asked to perform cognitive tasks on a computer designed to assess your thinking ability and short-term memory. Following this, you will be asked to perform an exercise test that allows us to simultaneously measure your breathing and heart rate. You'll be given an orientation of the equipment involved in the test (i.e. how the treadmill, mouthpiece, etc. work). You will then participate in the exercise test by walking/running on a treadmill at a vigorous pace. You will have the chance to practice on the treadmill prior to testing. After the exercise test, we will also perform a dual energy X-ray absorptiometry (DXA) scan, which measures your bone density (thickness) and the amount of fat and lean (non-fat) tissue in your body. For this scan, you will be asked to lie flat on your back on a table as the scanning machine moves above your body. The DXA scan is like an X-ray and takes about 5-10 minutes. Due to unknown risks to a fetus, you should not have this test if you may be pregnant. Following this session, you will be given a 7-day food journal as well as an activity monitor for physical activity assessment. You will be asked to record your food intake and wear the activity monitor for 7 days. You will be asked to return the food journal and accelerometer when you return for your second laboratory visit. Finally, you will be receiving separate containers (including coolers) for urine and fecal/stool sample collection. We will provide you with the instructions on how to properly use each collection containers. The urine sample will be collected the morning of your day 2 visit. It is expected that your visit today/day 1 will take approximately 2.5 hours.

Between Days 1 and 2

You will be asked to collect one fecal sample (using containers and coolers provided on day 1) between today and your day 2 appointment and bring it to 124 Freer within 15 minutes after the bowel movement. Also, between today and your day 2 appointment, you will asked to go online and complete 3 questionnaires that will contain questions about your typical stress level and attitudes towards foods and eating habits. Further, you will be asked to wear the activity monitor and record your diet in the food journals for one week. You will be asked to bring the activity monitor and food journal with you when you return for your day 2 appointment.

Day 2

You will be asked to collect one urine sample (with container and cooler provided on day 1) during the morning of your scheduled day 2 visit and bring it with you to our laboratory. Further, on day 2, you will be asked to come to our laboratory following an overnight fast (at least 10 hours). During the fasting, you will be asked not to eat any foods and avoid drinking any caloric beverages (juice, sodas, milk). You will also be asked to refrain from drinking caffeinated beverages until your appointment on day 2. However, you will be allowed to drink water as needed. After you arrive at your appointment, you will participate in a series of computer-based cognitive tasks followed by a venous blood draw. We will also measure your blood pressure using a blood pressure cuff. During the cognitive tasks, you will be seated in a comfortable chair and have your brain activity recorded through the use of sensors placed on the scalp and face. The experimenter will explain where the sensors will be placed before attaching them. The sensors are both painless and harmless, and serve to merely record electrical signals that are naturally produced by the body. The tasks involve watching a series of symbols or figures that appear on a computer screen in front of you. You will be asked to press button(s) in response to the symbols or figures.

Following cognitive testing, you will have a small amount of blood drawn (approximately 4 tablespoons). Blood will be extracted through a vein in your arm. Prior to drawing any blood, we will ask you to consent to the blood draw again to confirm that you are comfortable with the procedure. Venous blood will be drawn from a vein in the arm by a research team member who is trained and certified as a phlebotomist. A blood draw will not be attempted more than twice if the first try is unsuccessful and no further attempts will be made. If you do not consent to a venous blood draw but are willing to have a 'finger-prick', capillary blood draw, the phlebotomist may draw blood in this way. A small amount of blood will be stored and later analyzed for genetic and biological markers that may be related to diet, body composition, and thinking.

Risks:

All the measurement techniques being used in this study have been previously used in research studies with adult populations and the risks associated with participating in this study are minimal. There are no known risks of the optical coherence tomography and macular densitometry. These techniques are routinely used in clinical and research settings. However, if your eyes feel tired or fatigued during these assessments we will allow you to take as many breaks as you need.

For the maximal exercise test, there is a chance of minor injury, possibly some discomfort/soreness, and overuse injuries. However, we do not anticipate for any major injuries to occur. There is also the extremely slim chance that sudden death or cardiac irregularities may occur while exercising. This is rare and the benefits of exercise are known to outweigh risks. Nonetheless, at all times there will be at least three staff members trained in First-Aid and certified in CPR. In addition, during the DXA scan, you will be exposed to a very small amount of radiation. As part of everyday living, everyone is exposed to naturally occurring background radiation and receives a dose of about 200 to 300 millirem (mrem) each year. The effective dose from the DXA x-ray procedure is about one (1) mrem. At this dose, no harmful effects of radiation have been documented, suggesting that the risk is negligible. Finally, there may be some discomfort associated with the blood draw process, but the blood donation procedure is very common and involves minimal risk. There is a one in five chance of bruising in the area of sampling. As with all invasive procedures there is a slight risk of inflammation and infection. This risk will be minimized by the use of sterile procedures and equipment at all times. There is also a possibility of dizziness and lightheadedness associated with blood draws. However, you will be seated or lying down during and immediately following the blood draw, which will reduce the possibility of injury from a fall. These risks will also be minimized because a trained phlebotomist will conduct the blood draw.

In the Event of Injury:
In the unlikely event of physical injury resulting from this research study, immediate medical treatment is available from a number of health care providers in the area. However, the University of Illinois does not provide medical or hospitalization insurance coverage for participants in this research study, nor will the University of Illinois provide compensation for any injury sustained as a result of participation in this research study, except as required by law. If at any time, day or night, you experience adverse physical symptoms, you should immediately contact your personal physician or emergency personnel (i.e., dial 911).

Benefits:
There is no medical benefit to individuals who take part in this study. We do, however, consider the possibility that your participation in this project will contribute further to our understanding of the relationships between lifestyle behaviors, metabolic risk, gut health, and cognitive function. We hope the information learned from this study will benefit the general public by providing information about how the brain and gut are connected and whether diet and exercise can play a role in improving not only physical, but mental health as well.

Privacy and Rights:
Confidentiality is assured for all participants with regard to any responses and information provided. All data collected will be coded using numbers so that no individual data will be identifiable. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used. Personal information may be given out only if required by law. Organizations that may look at and/or copy your information and responses for research, quality assurance, and data analysis include:

- Government representatives, when required by law
- University of Illinois at Urbana-Champaign Institutional Review Board

When we study the DNA from your blood samples, we will also generate data about your entire genetic code. Despite the measures we take to protect this data and its link to your identity, and although there is now a federal law that prohibits genetic discrimination in health insurance and employment, there is a small risk that somebody could learn some genetic information about you from this study and then try to use it to discriminate against you or your family members in some way. For example, genetic data from this study could possibly be used by a disability, life, or long term care insurance company to deny you coverage, or by law enforcement officials to learn more about you or your family members for the purpose of a criminal investigation. The risk of this happening is currently very small, but as technology advances, there may be new ways to do this that we cannot foresee now.

Participation in this project is voluntary and you are free to withdraw your participation without penalty at any time.

Cost:
Participation in this study is free. As an incentive for your participation in the study, you will receive a gift card for $75 upon full completion of the study. If you decide to withdraw from the study prior to completing day 2 procedures, you will receive $25. This would be contingent upon completing day 1 procedures and providing one fecal sample.

Voluntariness:
When you sign this document, you are stating that the experiment has been fully explained to you, and that you understand that the data obtained from this study are to be used for research purposes only, not for the evaluation or diagnosis of any disorder, and that such data will remain confidential, except as required by law. You are also stating that you have had the opportunity to ask questions concerning any and all aspects of the procedures involved, that you are aware that participation is voluntary, and that you may withdraw your consent at any time. Your decision to participate, decline, or withdraw from participation will have no effect on your future relations with the University of Illinois.

You will be given a copy of this consent form for your records. If at any time (before, during, or after participation) you have a question, you are free to ask it, and you may contact the principal investigator, Dr. Naiman Khan (217-333-3893), nakhan2@illinois.edu), who is responsible for this study. If you wish to speak with someone specifically about complaints or concerns regarding *rights as a participant* in this study, you may contact the University of Illinois Institutional Review Board (217) 333-2670 (E-mail: irb@illinois.edu).

Before you agree to participate, please check each box to indicate that you:

- ☐ Understand the procedure.
- ☐ Give your consent voluntarily.
- ☐ Know that you can withdraw your consent at any time.

I the undersigned, hereby consent to be a participant in the project and undergo testing conducted in the Department of Kinesiology and Community Health at the University of Illinois for the following procedures:

- ☐ Maximal exercise test
- ☐ Venous blood draw
- ☐ Fecal samples will be stored and coded samples may be provided to other UIUC investigators
- ☐ Blood samples will be stored and coded samples may be provided to other UIUC investigators

I the undersigned, hereby consent to be a participant in the project described above conducted in the Department of Kinesiology and Community Health at the University of Illinois.

Participant's Name (Printed): _____

Participant Signature: _____ Date: _____

Signature of experimenter: _____ Date: _____

May we contact you in the future with information about future studies that may be of interest to you?

*Yes*_____ *No*_____

University of Illinois at Urbana-Champaign
Institutional Review Board

Approved: 1-20-17
Expires: 8-4-17
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Investigating the Effects of Avocado Intake on Metabolism and Cognition: A Systems Approach

Participant Consent Form

Investigators Directing Research:
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You are invited to participate in a research study that will help us understand the relationship between diet, gut function, metabolism, and thinking ability. This form will provide you with information about the study.

If you choose to participate, your involvement in this study will last for about 15 weeks. Today is the first of 8 laboratory visits along with 24 brief meal pick-up visits. Visits will last between 15 minutes (for meal pick up) and 3 to 3.5 hours (for one baseline testing session and one 12-week visit). If you agree to take part in this study, you will eat a pre-prepared meal once a day for 12 weeks. During this time we will measure your eye and metabolic health. We will also ask you to wear a physical activity monitor, complete study questionnaires, perform cognitive tasks, collect six fecal samples, collect 2 urine samples, and record your diet and fluid intake. Before we can collect any data, it's important to confirm that you:

1. Are informed about the procedures and their risks
2. Give your consent voluntarily (i.e., participate because you want to)
3. Know that you can withdraw your consent at any time
4. Are between 25-45 years old
5. Do not have any known food allergies

The procedures and the potential risks and/or benefits are provided below.

What You Will Do in the Experiment:

Baseline Period/Before Study Start:
Baseline Testing Day 1 (Today)
First we will ask you to complete brief health questionnaires and measure your height and weight to assess whether you qualify to be part of this study. We will inform you immediately whether or not you qualify for the study based on the information we collect. If you do not qualify, we will not keep any of your information and you will not receive any payment. We will ask you to answer questions about your medical history so we can evaluate your current health. This will help us determine if you are a good fit for this study and if it is safe for you to participate. We would like to know what medications you take now or have been taking to determine whether you qualify for the study. It is important that

we know about your medications since they can affect your metabolism. We will ask you to complete questionnaires to measure your usual diet intake. Your height and weight will also be measured. You will be asked to complete questionnaires to assess your sleep patterns, attitudes towards eating, and stress and anxiety. You will then be asked to look into a scope for a few minutes and observe and respond to a flickering blue light. We will also ask you to undergo an eye scan. During this scan you will be seated in front of an eye scanner and will be asked to rest your head on a support to keep it still. The scanner will then take an image of the eye without touching it. Scanning typically takes 10-15 minutes. Following this we will measure your visual function by asking you to read letters of different sizes on a chart. These tests will allow us to measure your eye health. After this, we will ask you to complete a task on a computer designed to test your memory. You will be given a 7-day food journal and an activity monitor. You will be asked to record your food intake and wear the physical activity monitor for 7 days. You will be asked to return these items when you return for your next visit. Finally, you will receive containers for stool sample collection. You will be asked to collect one fecal sample and bring it to Freer Hall within 15 minutes after passing. You will also be asked to collect one urine sample on the morning of your next scheduled testing visit. We will provide you with instructions on how to use the collection containers. Overall, we expect today's visit will take about 2.0 hours.

Baseline Testing Day 2

On day 2, you will be asked to come to our laboratory after an overnight fast (at least 10 hours). During the fasting, you will be asked not to eat any foods and or drink anything except water. You will also be asked to refrain from drinking caffeinated beverages during the fast. At the start of your visit, you will be seated in a comfortable chair and your brain activity will be recorded using sensors placed on your scalp and face. A trained staff member will explain where the sensors will be placed before attaching them. The sensors are both painless and harmless, and serve to record electrical signals that are naturally produced by the body. You will then be asked to take part in tasks that involve watching a series of symbols or figures that appear on a computer screen in front of you. You will be asked to press button(s) in response to the symbols or figures. You will then be asked to undergo a glucose tolerance test. For this test you will drink a glucose test beverage and have a catheter inserted into a vein in your arm. The catheter will be inserted with the help of a small needle, which will then be removed. Once the needle is removed, you should feel no sensation from the catheter. A small amount of blood will be collected through the arm catheter before you drink the glucose beverage (0 min) and five times (30, 45, 60, 90, 120 min) afterward. A total of 6 blood samples will be collected for a total amount of ~40 ml of blood. This is around 1/8th of the amount removed during a routine blood donation. After each blood sample is collected, the catheter will be "flushed" with a sterile saline solution in order to prevent blood from clotting in the catheter. A small amount of blood will also be collected (about 4 tablespoons) to measure other health markers such as cholesterol. A small amount of blood will be stored and later analyzed for genetic and biological markers that may be related to diet, body fat, and thinking. Venous blood will be drawn by a trained member of the research team. A topical anesthetic will be applied to your arm before the catheter is inserted. It is expected that your day 2 baseline visit will take 3.5 hours.

Baseline Testing Day 3

On day 3, you will be asked to come to our laboratory after an overnight fast (at least 10 hours). During the fasting, you will be asked not to eat any foods and or drink anything except water. You will also be asked to refrain from drinking caffeinated beverages during the fast. During this visit, we will measure waist circumference and ask you to lie flat on your back on a bone and body composition scanner called DEXA. The DEXA scan uses a small amount of X rays and takes about 5-10 minutes. Due to unknown risks to a fetus, you should not have this test if you may be pregnant. After this, we will measure how much energy your body uses while at rest. For this test you will be asked to lie quietly on a bed in a room for 45 minutes. During this time, there will be a clear canopy over your head and shoulders that will measure the amount of carbon dioxide in your breath. Next, we will look at your liver using an ultrasound machine. This machine is similar to what doctors use to look at babies within the womb. We will place a small amount of gel on your stomach to help us get a clearer picture. This gel is hypoallergenic and washes off very easily. We will then place a small wand-shaped instrument on your stomach. This will allow us to look directly at your liver. Images of your liver will be recorded on a video screen. These tests are for research purposes only and a physician will not be reviewing the results. If any problems with your liver are discovered (a mass, for example) your primary care physician will be notified. This scan will take approximately 10 minutes. Next, we will measure your blood pressure using a blood pressure cuff. Finally, we will

ask you to complete a task on a computer designed to test your memory. Overall, we expect today's visit will take 2 hours.

Intervention Period:
After you have completed baseline testing days, you will be asked to consume a test meal once each day for 12 weeks. The meals will be pre-prepared and contain food items that are typically found in the diet of most Americans (e.g., meats, dairy, legumes, grains, fruits, and vegetables). These meals will be ready for you to eat so you will not need to cook anything. You will be asked to visit Freer Hall to pick up your meals at least twice a week (no more than 10 minutes at a time). You will be asked to record your consumption (yes/no, amount consumed) on the dietary record.

During the 12-week study period, we will ask you to visit our laboratory for testing once a month (i.e., at 4 weeks and 8 weeks). During these visits, we will have you repeat the computer tasks completed on the baseline testing days, a blood draw without the placement of a catheter, the eye test described above, and the DEXA scan. You will also be asked to keep a 7-day food journal and provide one fecal sample during the 4th and 8th week of the study (described above).

Post-Intervention/Conclusion:
At the end of the 12-week period, we will ask you to return to the lab for 3 final visits. The procedures for these 3 visits will be identical to those described for baseline visits 1, 2 and 3.

Risks:
This is a low risk study. All the measurement techniques are commonly used in research studies with adults and the risks are minimal. However, the possible risks are detailed below. There are no known risks of the eye test, but it is possible that your eye may become strained or tired. To minimize this, you can take breaks as needed. During the body scan, you will be exposed to a very small amount of radiation. As part of everyday living, everyone is exposed to naturally occurring radiation that results in a dose of about 200 to 300 millirem (mrem) each year. The effective dose from the DEXA procedure is about one (1) mrem. At this dose, no harmful effects of radiation have been documented, suggesting that the risk is slight. There is no known risk of ultrasound exposure which you incurring during the scan of your liver. NOTE: the ultrasound and DXA scans are not used for diagnostic purposes and we are unable to diagnose disease using the results from your scans; however, you will receive a copy of your scans at the end of the study and we encourage you to share them with your physician.

There may be long-term effects of radiation exposure from DEXA to a fetus. Therefore, if I am pregnant, think I might be pregnant, or am trying to become pregnant I will not be scanned. My initial here indicates that I have no reason to believe I am pregnant at this time AND I am not planning on becoming pregnant over the course of this study.
Initial here _____

There may be some discomfort related to the blood draws and the oral glucose tolerance test, but the blood donation procedure is very common and low risk. There is a one in five chance of bruising where the blood is collected. As with all invasive procedures there is a slight risk of inflammation and infection. There is also an extremely slim chance of sudden death during the blood draws. This risk will be minimized by the use of sterile procedures and equipment at all times. There is also a possibility of dizziness and lightheadedness associated with blood draws. You will be seated or lying down during and after the blood draw to reduce risk of falling. All staff members are trained in First-Aid and certified in CPR. Finally, although it is rare, some people are allergic to avocados. Symptoms of an avocado allergy may include itching, swelling, and swallowing difficulties. In addition to avocados, the meals you will be asked to eat will include other foods that some people are allergic to, including nuts, eggs, dairy, soy, wheat, and fish. If you have any known food allergies, you should not participate in this study.

In the Event of Injury:
In the unlikely event of physical injury resulting from this research study, immediate medical treatment is available from health care providers in the area. However, the University of Illinois does not provide medical or hospitalization insurance coverage for participants in this study, nor will the University of Illinois provide compensation for any injury sustained as a result of participation in this research study, except as required by law. If at any time, day or night, you

have adverse physical symptoms, you should immediately contact your personal physician or emergency personnel (i.e., dial 911).

Benefits:
There is no medical benefit of taking part in this study. However, participation may contribute to our understanding of how diet, metabolic risk, gut health, and thinking are related. We hope the information learned from this study will benefit the general public by providing information about how the brain and gut are connected.

Confidentiality
Will my study-related information be kept confidential?
Yes, but not always. In general, we will not tell anyone any information about you. When this research is discussed or published, no one will know that you were in the study. However, laws and university rules might require us to tell certain people about you. For example, your records from this research may be seen or copied by the following people or groups:

- Representatives of the university committee and office that reviews and approves research studies, the Institutional Review Board (IRB) and Office for Protection of Research Subjects;
- Other representatives of the state and university responsible for ethical, regulatory, or financial oversight of research;
- Federal government regulatory agencies such as the Office of Human Research Protections in the Department of Health and Human Services
- The financial sponsor of the research, the Haas Avocado Board

Some samples obtained during this study will be stored in the laboratory (maximum 15 years), and may be used for further research. These extra samples are used for analyses that need to be repeated. Also, when publishing, reviewers often ask for additional measures and these samples could be used for this as well. Instead of contacting you later, you are asked to indicate whether you will permit these samples to be used in future research by selecting the appropriate option at the bottom of this form.

Privacy and Rights:

Confidentiality is assured for participant's responses and information. Data will be coded using numbers so that no individual data will be identifiable. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used. Personal information may be given out only if required by law. Organizations that may look at and/or copy your information and responses for research, quality assurance, and data analysis include:

- Government representatives, when required by law
- University of Illinois at Urbana-Champaign Institutional Review Board

Participation in this project is voluntary and you are free to withdraw your participation without penalty at any time.

Cost:
There is no cost to participate in this study. As an incentive for your participation, you will receive a gift card for $50 after completion of testing weeks 4, $100 at week 8, and a gift card for $200 will be provided upon full completion of the study.

Voluntariness:
When you sign this document, you are stating that the study has been fully explained to you, and that you understand that the data from this study are to be used for research purposes only, not for the evaluation or diagnosis of any disorder, and that such data will remain confidential, except as required by law. You are also stating that you have had the opportunity to ask questions about the procedures, that you are aware that participation is voluntary, and that you may withdraw your consent at any time. Your decision to participate, decline, or withdrawal will have no effect on your future relations with the University of Illinois.

You will be given a copy of this consent form for your records. If at any time (before, during, or after participation) you have a question, you are free to ask it, and you may contact the principal investigators, Dr. Hannah Holscher (217-300-2512, hholsche@illinois.edu) and Dr. Naiman Khan (217-300-1667), nakhan2@illinois.edu), who are responsible for this study. If you wish to speak with someone about complaints or concerns about your *rights as a study participant*, you may contact the University of Illinois Institutional Review Board (217) 333-2670 (E-mail: irb@illinois.edu).

Before you agree to participate, please check each box to indicate that you:

☐ Understand the procedure.

☐ Give your consent voluntarily.

☐ Know that you can withdraw your consent at any time.

☐ Have no known food allergies.

I the undersigned, hereby consent to be a participant in the project and undergo testing conducted in the Department of Kinesiology and Community Health and the Department of Food Science and Human Nutrition at the University of Illinois for the following procedures:

☐ Venous blood draws

☐ Oral glucose tolerance tests

☐ Fecal, blood, and urine samples will be stored and coded samples may be provided to other UIUC researchers

☐ Additional analyses on the samples collected may be conducted at a later time

I the undersigned, hereby consent to be a participant in the project described above conducted in the Department of Kinesiology and Community Health and the Department of Food Science and Human Nutrition at the University of Illinois.

Participant's Name (Printed): _____

Participant Signature: _____ Date: _____

Signature of experimenter: _____ Date: _____

May we contact you in the future with information about future studies that may be of interest to you?

*Yes*_____ *No*_____

University of Illinois at Urbana-Champaign
Institutional Review Board

Approved: 1-20-17
Expires: 11-17-17
IRB #: 16677